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nature reviews rheumatology

UCTD OR EARLY SLE?

Evolving perceptions, diagnostic challenges and clinical implications

Global epidemiology of vasculitis

Incidence and prevalence patterns

The Musculoskeletal Knowledge Portal: improving access to multi-omics data

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Built by and for the research community, the Musculoskeletal Knowledge Portal (MSK-KP) offers researchers a single integrated platform on which to display, access, distill and explore results from large genomic and epigenomic studies to formulate hypotheses and accelerate the development of patient-centered therapeutics for complex, multi-factorial conditions such as osteoarthritis.

Musculoskeletal diseases include more than 150 conditions and are a leading cause of chronic disability[1]. The development of genotyping and sequencing technologies and computational resources for assembling genomes over the past two decades has produced an unprecedented opportunity to decipher the genetic and epigenetic underpinnings of disease. At the present time, genomic information is rarely used for diagnosing musculoskeletal diseases and is limited to early-onset forms and monogenic syndromes. This gap in applying genomic information prevents early diagnosis and treatment of musculoskeletal diseases. Without genetically determined targets, large phase II and III clinical trials of biologic agents might be less likely to succeed. The Musculoskeletal Knowledge Portal (MSK-KP) aims to bridge this gap by making genomic data relevant to musculoskeletal diseases accessible to the public.

Launched in March 2020, the MSK-KP provides a single integrated platform by which to display and rapidly explore omics data[2] (FIG. 1). The MSK-KP is a collaborative effort between the Broad Institute's Knowledge Portal Network, which is powered by the Human Genetics Amplifier (HuGeAMP) software platform, and the big data working group from the International Federation of Musculoskeletal Research Societies (IFMRS). The MSK-KP is currently populated with over 255 datasets for 282 traits. The first musculoskeletal data on the portal were from genome-wide association studies (GWAS) on bone mineral density and fractures related to osteoporosis. Data on skeletal muscle strength and paediatric musculoskeletal traits are also now available, and there are plans to include data on rheumatoid arthritis and other joint diseases. The first data on osteoarthritis from the arcOGEN and GERA studies[3,4] were added in late 2020, as were assay for transposase-accessible chromatin with sequencing (ATAC-seq) data[5]. New data from the Genetics of Osteoarthritis Consortium will be available on the MSK-KP in October 2021 (REF.[6]).

Going beyond GWAS with the MSK-KP

Although GWAS have provided unbiased insights into variants and genomic regions associated with disease, they have limited ability to demonstrate causality or to separate variants associated with disease initiation and those linked to disease progression. Up to 90% of variants occur in non-coding regions of the genome, and 75% of variants associated with osteoarthritis appear in enhancer regions where DNA binding factors contribute to the expression of genes that can lie near or far from the variant[7]. Methods encoded by the MSK-KP can generate a list of transcription factors whose DNA binding might be affected positively or negatively by a variant or alternative allele of choice[8], thereby enabling hypothesis-driven mechanistic research into how gene variants control gene expression. The MSK-KP therefore represents a valuable tool that allows all scientists to access and distill results from large genomic and epigenomic studies.

The wealth of human genomic information on the MSK-KP can be easily queried. Data for musculoskeletal disease phenotypes such as osteoarthritis, osteoporosis and bone mineral density can be accessed from the MSK-KP homepage. The MSK-KP generates the list of genes nearest to phenotype-associated variants and houses a list of potential 'effector genes' for the phenotype. Alternatively, specific genes, chromosome regions or variants can be queried. For example, entering the reference single nucleotide polymorphism cluster identification number for a genetic variant into the portal will yield associations with a variety of traits related to anthropometric, cardiovascular, glycemic, lipid, musculoskeletal, nutritional, renal, and sleep or circadian phenotypes. The MSK-KP automatically

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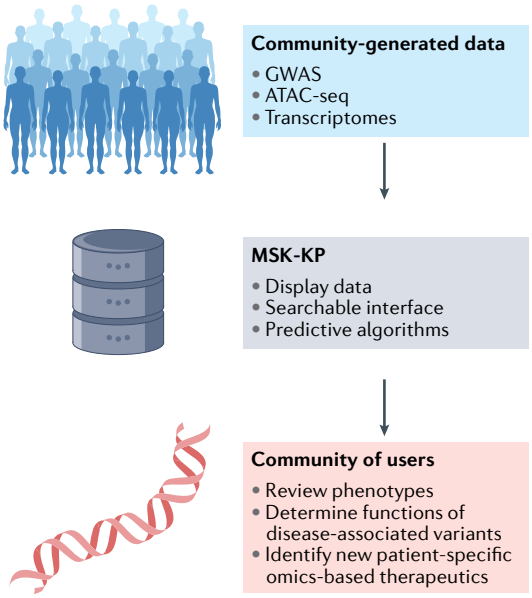

Fig. 1 | **The Musculoskeletal Knowledge Portal serves the research community.** The Musculoskeletal Knowledge Portal (MSK-KP) is a gateway to data from genome-wide association studies (GWAS) and other omics data. Data generated by the musculoskeletal research community can be queried by gene name, variant or phenotype to identify functions of disease-associated variants. Tracks for epigenomic information can be displayed to further understand variant functions. ATAC-seq, assay for transposase-accessible chromatin with sequencing.

generates plots so that positive and negative associations between a variant allele and a particular trait can easily be visualized. The resulting information can be used to generate new hypotheses, test old hypotheses and generate information for grant applications, manuscripts and presentations. Importantly, the MSK-KP stores the full underlying data and their sources as a public resource without revealing identifying or protected information.

A call to action

The IFMRS big data working group, of which we are members, is interested in fostering collaborations and developing new computational tools that integrate non-genomic data, including single-cell RNA sequencing, gene ontogeny, proteomics, metabolomics and animal phenotypes, into the MSK-KP interface to accelerate discovery and therapeutic development. To this end, the IFMRS working group has recently established collaborations with the leaders of the musculoskeletal Human Cell Atlas network[9] and Bonebase. We are also integrating new tools that can link human or murine gene expression with gene variants from human GWAS.

We would like to invite all readers and investigators to contribute the results of their studies to the MSK-KP. Presently, less than 3% of participants in GWAS on osteoarthritis are of non-European ancestry[6], so studies with greater diversity are especially needed. The MSK-KP does not share identifying or protected information; it only reports the results in the way intended by the contributor. We also ask readers to submit data to the other portals listed above and to the Single Cell Portal (for RNA transcript data) regardless of the model system used to facilitate integration into the MSK-KP and to disseminate knowledge. Finally, we ask readers and funding agencies to support the development of computational tools that bring user-friendly platforms to the community. Doing so will accelerate the development of machine learning and artificial intelligence platforms that integrate omics data with electronic health records and social determinants of musculoskeletal health. Such advances could lead to the functional characterization of key variants and gene products in musculoskeletal diseases and, ultimately, to new diagnostic and therapeutic avenues for musculoskeletal diseases.

In conclusion, the MSK-KP offers researchers an unprecedented means to access genomic data to formulate hypotheses with the goal of generating and testing patient-centered therapeutics for complex, multi-factorial musculoskeletal conditions. As part of a larger Knowledge Portal network, the MSK-KP enables studies of pleiotropy and unexpected relationships between disease processes. This feature is particularly valuable for the study of chronic diseases such as osteoporosis and osteoarthritis, in which multiple morbidities including obesity, diabetes and heart disease are present and genetic contributions are complex. We thank the teams that have contributed content and results so far, and welcome more submissions.

1. Sebbag, E. et al. The world-wide burden of musculoskeletal diseases: a systematic analysis of the World Health Organization Burden of Diseases Database. *Ann. Rheum. Dis.* **78**, 844–848 (2019).
2. Kiel, D. P. et al. The Musculoskeletal Knowledge Portal: making omics data useful to the broader scientific community. *J. Bone Miner. Res.* **35**, 1626–1633 (2020).
3. Tachmazidou, I. et al. Identification of new therapeutic targets for osteoarthritis through genome-wide analyses of UK Biobank data. *Nat. Genet.* **51**, 230–236 (2019).
4. Guindo-Martinez, M. et al. The impact of non-additive genetic associations on age-related complex diseases. *Nat. Commun.* **12**, 2436 (2021).
5. Richard, D. et al. Evolutionary selection and constraint on human knee chondrocyte regulation impacts osteoarthritis risk. *Cell* **181**, 362–381 (2020).
6. Boer, C. G. et al. Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations. *Cell* **184**, 4784–4818 (2021).
7. Muthuirulan, P. et al. Joint disease-specificity at the regulatory base-pair level. *Nat. Commun.* **12**, 4161 (2021).
8. Kheradpour, P. & Kellis, M. Systematic discovery and characterization of regulatory motifs in ENCODE TF binding experiments. *Nucleic Acids Res.* **42**, 2976–2987 (2014).
9. Baldwin, M. J. et al. Mapping the musculoskeletal system one cell at a time. *Nat. Rev. Rheumatol.* **17**, 247–248 (2021).

Competing interests
D.P.K. declares he has received grant funding to his institution from Amgen, Radius Health and Solarea Bio; serves on scientific advisory boards for Pfizer and Solarea Bio; and has received royalties for publication in UpToDate from Wolters Kluwer. The other authors declare no competing interests.

RELATED LINKS
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Knowledge Portal Network: https://kp4cd.org/
Musculoskeletal Knowledge Portal: https://msk.hugeamp.org/
Single Cell Portal: https://singlecell.broadinstitute.org/single_cell

OSTEOARTHRITIS

Articular cartilage hypoxia is a potential target for OA therapy

The histone methyltransferase DOT1L is known to have a protective effect on joints in osteoarthritis (OA). In a new study, identification of an association between DOT1L expression and hypoxia has revealed a potential therapeutic target for OA.

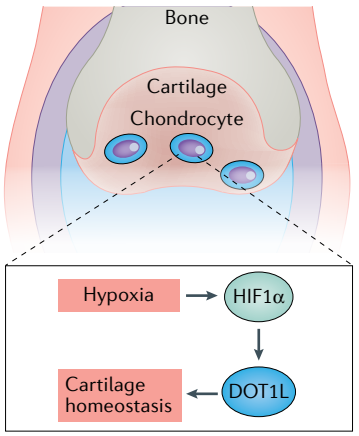
DOT1L contributes to epigenetic transcriptional regulation by methylation of lysine residue 79 of histone H3 (H3K79), and in OA its activity is lower in damaged cartilage than in undamaged cartilage. The link between reduction of DOT1L activity and the onset of OA has been demonstrated in mice in studies of pharmacological inhibition and genetic knockout. "These studies made it clear that maintaining DOT1L function is key to preserving joint health," explains Silvia Monteagudo, corresponding author on the new study. "However, the DOT1L-regulating molecules and networks have remained elusive."

To investigate the regulation of DOT1L, Monteagudo and colleagues developed a bioinformatics pipeline to identify transcription factors with potential for specific binding to the *DOT1L* promoter. Among them was hypoxia-inducible factor-1α (HIF1α), which is known to promote cartilage homeostasis. "This finding made sense to us, because in healthy conditions, cartilage is hypoxic, but this changes in OA," adds Monteagudo.

> "hypoxia was positively associated with DOT1L expression, HIF1α stabilization and H3K79 methylation"

The researchers tested the association between hypoxia and DOT1L by treating human articular chondrocytes with hypoxia mimetics or growing them in hypoxic conditions. In these experiments, hypoxia was positively associated with *DOT1L* expression, HIF1α stabilization and H3K79 methylation. Hypoxia also induced expression of *COL2A1* and *ACAN*, which encode type II collagen and aggrecan, respectively, and are markers of chondrocyte health.

Notably, induction of OA in mice by destabilization of the medial meniscus resulted in reduced expression of HIF1α and DOT1L and reduced H3K79 methylation.



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Intra-articular injection of a hypoxia mimetic reversed these changes, and reduced cartilage damage, osteophyte formation and synovial inflammation compared with vehicle-only treatment. "Restoring hypoxia in the joint by local administration of selective hypoxia mimetics could be an attractive therapeutic strategy for OA, as it restores DOT1L function in articular cartilage," concludes Monteagudo.

Robert Phillips

ORIGINAL ARTICLE De Roover, A. et al. Hypoxia induces DOT1L in articular cartilage to protect against osteoarthritis. *JCI Insight* https://doi.org/10.1172/jci.insight.150451 (2021)

SPONDYLOARTHRITIS

Pathogenic role for MIF likely in SpA

Macrophage migration inhibitory factor (MIF) has previously been linked to inflammation and new bone formation in ankylosing spondylitis, a prototypic form of spondyloarthritis (SpA). Now, a new study has revealed how MIF exerts its pathogenic role in experimental SpA, providing a hypothesis for how MIF might function in patients with SpA.

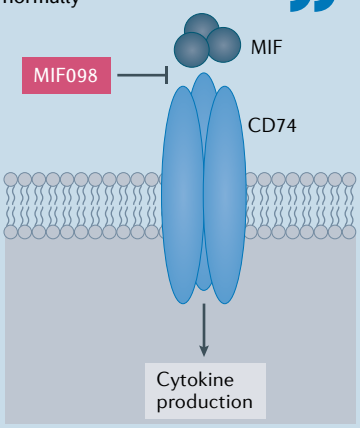
"The studies were done in a preclinical animal model of SpA, the SKG mouse model, that manifests joint, skin and eye inflammation," explains first author Akihiro Nakamura. "We found that MIF is increased in this animal model when the mice develop SpA."

The cells responsible for producing MIF in SKG mice treated with curdlan (which triggers an accelerated form of disease) were neutrophils, which were present in increased numbers at sites of inflammation. Similarly, neutrophils from patients with SpA produced more MIF than neutrophils from healthy individuals, suggesting that neutrophils could be a main source of MIF in SpA.

"Interestingly we also found that MIF can change the functioning of regulatory T (T_{reg}) cells that normally control inflammation," says Nakamura. "MIF can facilitate T_{reg} cells to acquire a pathogenic T helper 17 cell-like phenotype that is responsible for the production of the pro-inflammatory cytokine IL-17, which is a well-known player in SpA inflammation."

To test the therapeutic potential of reducing MIF,

> "treatment with MIF098 reduced new bone formation and the severity of arthritis and dermatitis"



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Nakamura and colleagues tested an antibody that targets neutrophil function and a small-molecule antagonist that blocks interaction between MIF and its receptor CD74 (MIF098). Blocking MIF-producing neutrophils in curdlan-treated SKG mice delayed the progression of clinical features of SpA. In addition, both prophylactic and therapeutic treatment with MIF098 reduced new bone formation and the severity of arthritis and dermatitis in these mice.

"We are now working to understand the mechanisms behind the actions of MIF on new bone formation associated with SpA," states corresponding author Nigil Haroon. "We are also pursuing further studies on MIF inhibition in SpA. We hope to bring this to the clinic sometime in the future."

Joanna Clarke

ORIGINAL ARTICLE Nakamura, A. et al. Macrophage migration inhibitory factor drives pathology in a mouse model of spondyloarthritis and is associated with human disease. *Sci. Transl Med.* **13**, eabg1210 (2021)
RELATED ARTICLE Kang, I. & Bucala, R. The immunobiology of MIF: function, genetics and prospects for precision medicine. *Nat. Rev. Rheumatol.* **15**, 427–437 (2019)

IN BRIEF

OSTEOARTHRITIS

Knee OA progression risk with steroids or HA

Data from the OAI and MOST prospective cohort studies indicate that use of intra-articular injections of corticosteroids is not associated with an increased risk of knee osteoarthritis (OA) progression as compared with use of hyaluronic acid (HA) injections. Radiographic progression rates were similar in the knees of patients who used corticosteroid injections ($n = 629$) or HA injections ($n = 162$), as assessed by joint space narrowing, Kellgren–Lawrence grade and medial joint space width.

ORIGINAL ARTICLE Bucci, J. et al. Progression of knee osteoarthritis with use of intra-articular corticosteroids vs. hyaluronic acid. *Arthritis Rheumatol.* https://doi.org/10.1002/art.42031 (2021)

CLINICAL TRIALS

Antibiotics keep rheumatic heart disease at bay

Secondary antibiotic prophylaxis reduced the risk of progression of latent rheumatic heart disease in children and adolescents 5–17 years old in a randomized controlled trial. Of the 799 participants who completed the GOAL trial in northern Uganda, 3 of 399 (0.8%) of those who received intramuscular injections of penicillin G benzathine every 4 weeks had echocardiographic progression at 2 years, compared with 33 of 400 (8.2%) of those who received no prophylaxis (risk difference −7.5%; 95% CI −10.2 to −4.7; $P < 0.001$). Two participants had serious adverse events attributable to the antibiotic treatment.

ORIGINAL ARTICLE Beaton, A. et al. Secondary antibiotic prophylaxis for latent rheumatic heart disease. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2102074 (2021)

PSORIATIC ARTHRITIS

Guselkumab effective through 2 years in PsA trial

New results from the phase III DISCOVER-2 trial ($n = 739$) indicate that the benefits of continued treatment with guselkumab are maintained over 2 years in patients with active psoriatic arthritis (PsA) and no previous biologic DMARD therapy. Treatment with guselkumab, which targets the p19 subunit of IL-23, improved several disease domains including skin and joint symptoms, with similar response rates across both treatment regimens assessed (guselkumab 100 mg every 4 or 8 weeks). Rates of radiographic progression remained low and no new safety signals were observed.

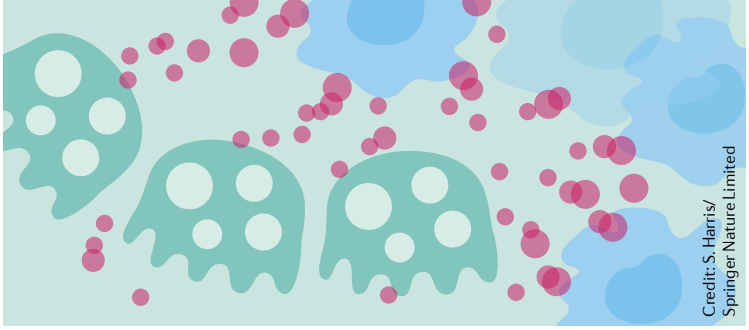
ORIGINAL ARTICLE McInnes, I. B. et al. Long-term efficacy and safety of guselkumab, a monoclonal antibody specific to the p19 subunit of interleukin-23, through 2 years: results from a phase 3, randomized, double-blind, placebo-controlled study conducted in biologic-naive patients with active psoriatic arthritis. *Arthritis Rheumatol.* https://doi.org/10.1002/art.42010 (2021)

SPONDYLOARTHRITIS

Secukinumab might improve enthesitis in SpA

In the phase IIIb ACHILLES study of patients with spondyloarthritis (SpA; $n = 204$), a greater proportion of patients who received the anti-IL-17A antibody secukinumab (150 mg or 300 mg) than those who received placebo reported resolution of Achilles tendon enthesitis at week 24, but the difference was not statistically significant ($P = 0.136$). Patients in the secukinumab group had greater improvements in heel pain and heel ensethopathy activity, which were sustained to week 52. Despite all patients having a clinical diagnosis of enthesitis, a substantial proportion did not have objective signs of inflammation on centrally read MRIs, suggesting a discrepancy between the clinical and imaging assessments.

ORIGINAL ARTICLE Behrens, F. Efficacy and safety of secukinumab in patients with spondyloarthritis and enthesitis at the Achilles tendon: results from a phase 3b trial. *Rheumatology* https://doi.org/10.1093/rheumatology/keab784 (2021)



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OSTEOPOROSIS

Somatic mutations linked to osteoporosis

Acquired genetic mutations, known as somatic mutations, occur throughout the lifetime of a cell and tend to accumulate with increasing age. Interest has therefore been growing about the potential role of somatic mutations in diseases that are more common in older individuals. According to a new study published in *The Journal of Experimental Medicine*, somatic mutations are associated with osteoporosis in humans and can directly cause bone loss in mice, suggesting a potentially causal role for somatic mutations in osteoporosis.

Somatic mutations in genes linked with epigenetic regulation (normally associated with myeloid cancers) can be found in haematopoietic cell clones present at low levels in otherwise healthy individuals — a state known as clonal haematopoiesis of indeterminate potential (CHIP). "The analysis of data from more than 110,000 individuals in the UK Biobank gave us a powerful insight that CHIP is associated with osteoporosis," states Peter Geon Kim, first author on the new study.

To test whether CHIP could directly cause bone loss, Kim and colleagues generated mice with haematopoietic deletion of *Dnmt3a*, one of the most commonly mutated genes in CHIP, and performed bone marrow transplants into wild-type mice. After 20 weeks, mice that had received *Dnmt3a*$^{-/-}$ bone marrow had reduced trabecular bone volume and cortical bone area, as well as increased osteoclast activity, compared with mice that received wild-type bone marrow. Similar results were obtained in mice that received bone marrow bearing the most common *DNMT3A* mutation found in CHIP.

Individuals with CHIP have an increased risk of cardiovascular disease, which is thought to be caused by the production of pro-inflammatory cytokines by macrophages with CHIP mutations. "With osteoporosis, we hypothesized that CHIP could either directly influence myeloid-derived bone-resorbing osteoclasts, or alternatively, pro-inflammatory cytokines from myeloid cells with CHIP mutations could indirectly influence osteoclasts," explains corresponding author Benjamin Ebert.

The researchers used in vitro differentiation assays and transwell assays to determine that the increase in osteoclast activity was linked to a soluble factor produced by *Dnmt3a*$^{-/-}$ macrophages. The results of a CRISPR screen suggested IL-20 as a candidate soluble factor that could be upregulated by the loss of epigenetic regulation by DNA methyltransferase 3A (encoded by *DNMT3A*). IL-20 was upregulated in the serum of *Dnmt3a*$^{-/-}$ mice compared with wild-type mice and was able to increase osteoclast differentiation in vitro; a process that could be blocked using an anti-IL-20 antibody. A role for IL-20 was confirmed in vivo when administration of an anti-IL-20 antibody reduced markers of bone turnover in mice transplanted with *Dnmt3a*$^{-/-}$ bone marrow.

"Our research suggests that CHIP has wide-ranging clinical consequences beyond promoting haematopoietic malignancy and cardiovascular disease," concludes Kim. In the future, Kim and colleagues hope to elucidate the mechanisms behind the effects of CHIP on inflammation.

Joanna Clarke

ORIGINAL ARTICLE Kim, P. G. et al. *Dnmt3a*-mutated clonal hematopoiesis promotes osteoporosis. *J. Exp. Med.* **218**, e20211872 (2021)
RELATED ARTICLE Karsenty, G. et al. Bone marrow runs the (bone) show. *J. Exp. Med.* **218**, e20211996 (2021)

RHEUMATOID ARTHRITIS

Erasing the memory of arthritis in joints

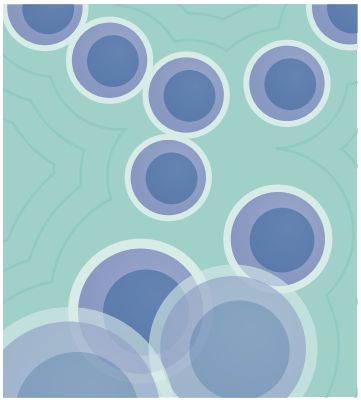
New research suggests that recurrence of arthritis is mediated by a population of resident memory T (T_{RM}) cells that accumulate in the synovium of affected joints, persist during remission and contribute to disease flare in the same joints following activation by antigen. The findings could help explain why individual patients develop a characteristic pattern of joint inflammation, and also suggest that depletion of synovial T_{RM} cells could ameliorate local disease recurrence.

Using three mouse models characterized by recurrent site-specific arthritis, the researchers showed that, in joints affected by arthritis, a small population of T cells remained in the joints during remission. These cells expressed a pattern of surface proteins and had metabolic features consistent with a T_{RM} cell phenotype and they did not migrate in response to the chemokine CCL21, which attracts T cells to secondary lymphoid organs. These characteristics, together with the cells' long-term retention and function in the synovium, enabled the researchers to identify them as T_{RM} cells.

The researchers then demonstrated how T_{RM} cells contribute to arthritis flares in mice. "T_{RM} cells nucleated recurrent inflammation upon stimulation by antigen, recruiting other effector T cells via CCL5, as reflected by abrogation of disease flare when this cytokine was blocked," reports corresponding author Peter Nigrovic. "Depletion of T_{RM} cells during remission markedly attenuated recurrent arthritis upon systemic antigen re-challenge," he adds. Together, the findings provide a mechanism for joint-specific memory and disease recurrence.

The researchers identified a similar population of $CD8^+$ T_{RM} cells in synovial tissue from patients with rheumatoid arthritis; in common with the T_{RM} cells from mice, these cells also prominently expressed CCL5 and exhibited a highly restricted T cell receptor repertoire.

> depletion of synovial T_{RM} cells could ameliorate local disease recurrence



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"Our data show why chronic disease can be so difficult to control and identify targeting of synovial T_{RM} cells as a new therapeutic avenue," says Nigrovic. "Our future efforts are directed to understanding how T_{RM} cells form and persist in arthritis tissue and to finding practical ways of targeting T_{RM} cells in humans."

Sarah Onuora

ORIGINAL ARTICLE Chang, M. H. et al. Arthritis flares mediated by tissue-resident memory T cells in the joint. *Cell Rep.* **37**, 109902 (2021)

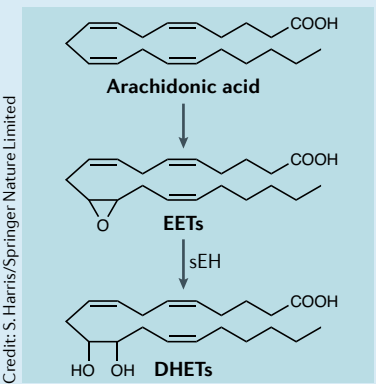
PAIN

Inhibition of epoxide hydrolysis targets pain in osteoarthritis

In a newly published study, researchers have identified an association between pain in osteoarthritis (OA) and *EPHX2*, which encodes soluble epoxide hydrolase (sEH). By inhibition of sEH, they have also demonstrated reversal of pain behaviour in a mouse model of OA.

In the absence of effective disease-modifying treatments for OA, NSAIDs enable palliative pain reduction through inhibition of the conversion of arachidonic acid to inflammatory prostanoids. However, some arachidonic acid derivatives, such as epoxyeicosatrienoic acids (EETs), have anti-inflammatory effects. EETs act by inhibiting NF-κB signalling. EETs are known to reduce inflammatory pain in a rat model, but their effects are limited by sEH, which converts EETs into dihydroxyeicosatrienoic acids (DHETs).

> targeting sEH could represent a new therapeutic approach for treatment of OA pain



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In the new study, researchers investigated the role of EETs and identified associations between several single-nucleotide polymorphisms (SNPs) in *EPHX2* and three clinical measures of pain in 318 individuals with knee pain. In a separate cohort of 92 individuals with knee OA, plasma concentrations of EETs were positively associated with pain measures, and in a third cohort of 62 participants with radiographic knee OA, concentrations of DHETs were also associated with measures of pain. "These data highlight how the sEH enzymatic pathway is perturbed in people with OA pain," explain Victoria Chapman, Peter Gowler and David Walsh, members of the team that carried out the study.

In a mouse model of OA induced by destabilization of the medial meniscus, the researchers found that both acute and chronic administration of an sEH inhibitor reduced pain behaviour and decreased concentrations of some DHETs compared with vehicle-only controls.

These findings suggest that targeting sEH could represent a new therapeutic approach for treatment of OA pain. Comments provided by the research team indicate that further work is required to determine whether pain-associated SNPs of *EPHX2* have functional consequences for sEH activity, whether DHETs are inert by-products of EET metabolism and whether sEH inhibition has disease-modifying effects in OA. In the meantime, we await the results of ongoing clinical trials of sEH inhibition for neuropathic pain.

Robert Phillips

ORIGINAL ARTICLE Gowler, P. R. W. et al. Clinical and preclinical evidence for roles of soluble epoxide hydrolase in osteoarthritis knee pain. *Arthritis Rheumatol.* https://doi.org/10.1002/art.42000 (2021)

RHEUMATOID ARTHRITIS

Passive smoking in childhood accelerates RA risk for smokers

Lars Klareskog

Smoking during adulthood is a known risk factor for seropositive rheumatoid arthritis (RA) but how exposure to passive smoking affects RA risk is uncertain. New data from the Nurses' Health Study on passive smoking over a lifetime suggest childhood exposure could be an important factor for future RA development.

Refers to Yoshida, K. et al. Passive smoking throughout the life course and the risk of incident rheumatoid arthritis in adulthood among women. *Arthritis Rheumatol.* https://doi.org/10.1002/art.41939 (2021).

Smoking is the only known major environmental risk factor for rheumatoid arthritis (RA) and is believed to exert its action via exposure of the lungs to smoke, resulting in an immune reaction that contributes to the onset of seropositive RA[1–3]. Although the effects of active smoking in adulthood on the risk of developing RA are well established, the role of passive smoking has been unclear; some reports have indicated a role for passive smoking in RA risk[4], whereas other studies have not found any such statistically significant effect[5]. Now, in a new study, Yoshida and colleagues[6] address the subject of passive smoking in a novel and interesting way by analysing the effects of passive exposure to tobacco smoke on RA risk from fetal life onwards.

To perform their analysis, Yoshida and colleagues[6] utilized data from the Nurses' Health Study II, which gave them access to very detailed information on passive as well as active smoking and many relevant co-variates from two large cohorts of more than 90,000 female nurses in the USA. They used a combination of self-reporting from the nurses on passive smoking during childhood and adulthood and active personal smoking during adulthood, and retrieved information on maternal smoking and diagnosis of 532 cases of RA (seropositive and seronegative) from medical records. Having access to this unique information on life-long exposure to passive, as well as active, smoking enabled the authors to analyse the effects of the different types of tobacco smoke exposure in utero, in childhood and in adulthood on the development of seropositive and seronegative RA. An inherent part of the design of the Nurses' Health Studies is the inclusion of only women, leaving it uncertain whether the results of this study[6] also pertain to men. However, most other studies on the effects of smoking on men and women have shown the same risk patterns[1–3], so it can be assumed that the same risks as shown by Yoshida et al.[6] for women would exist for men.

Using this approach, Yoshida and colleagues did not find any statistically significant effect of active maternal smoking during pregnancy on the fetus when adjusted for active smoking during adulthood[6]. By contrast, passive smoke exposure during childhood was associated with an increased risk of developing seropositive RA when active smoking in adulthood was accounted for. A methodological concern was that exposure to maternal smoking in utero was closely associated with exposure to passive smoking as a child, so that these two types of exposure could not be clearly separated, even though a statistically significant risk for RA was only found for the effects of passive smoking during childhood. Further stratification for smoking in adulthood showed that the risk conferred by exposure to passive smoking as a child was evident only for those who were active smokers as adults, and not for adult never-smokers.

The results of this study[6] further illustrate the notion that the emergence of the seropositive variant of RA — and probably most other immune-mediated diseases — should be studied and understood in the longitudinal perspective, taking environmental exposures in utero and during early childhood into account. Notably, other very early environmental exposures (such as infections during the first year of life) and birth weight have also been linked to an increased risk of RA[7,8], thereby further emphasizing the need to study several early environmental exposures as risk factors for RA.

> "the risk of RA from passive exposure to tobacco smoke during childhood was not increased in individuals who did not smoke at all as adults"

The mechanisms behind the finding reported by Yoshida et al. could not be analysed in this epidemiological setting, with the exception of the separation between seropositive and seronegative RA, for which effects of passive as well as active smoking on RA risk were consistently found only for the seropositive variant of the disease[6]. Nevertheless, the mechanisms can be speculated about, as the authors do when they suggest that their results might support the 'mucosal origins hypothesis', the idea that exposure to smoke in the lungs might trigger autoimmunity and the future development of seropositive RA[1,2]. However, the finding that the effects of tobacco smoke exposure on RA development in much later phases of life were enabled by early life events[6] also suggests that epigenetic mechanisms and early immunological imprinting might be of importance. Many previous studies have highlighted an interaction between smoking as an environmental risk factor and genetic factors, in particular MHC class II gene variants[9], and addition of genetic analysis to the current study[6] might have provided some additional clues to the mechanisms involved. However, no genetic data or gene–environment analyses were included in this study, possibly as a result of power issues.

From a prevention and public health perspective, the results from this study[6] further emphasize the importance of advocating a non-smoking environment (and society) as an important means of prevention for RA now that that there is evidence that smoking by parents might have long-term effects on RA risk for their children. The positive message from this study is that the risk of RA from

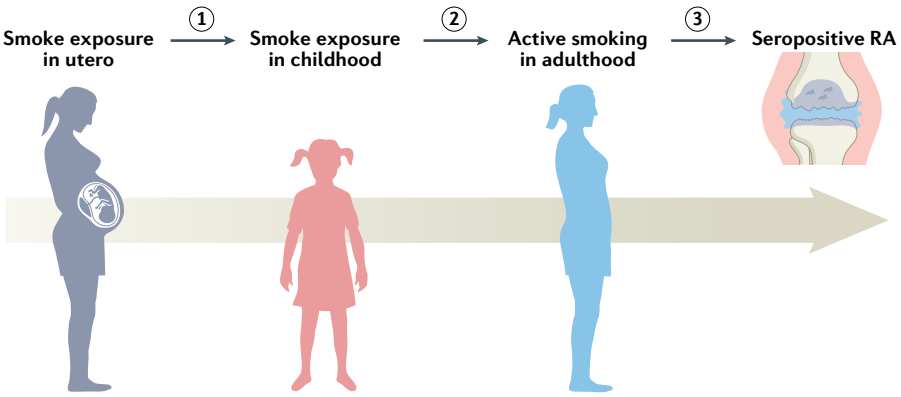

Fig. 1 | **Effects of passive and active smoking on the risk of RA over the life course.** Tentative view of how exposure to passive smoking in early life might influence the effects of active smoking on the risk of rheumatoid arthritis (RA) in adulthood. The arrows indicate how exposure to maternal smoking is associated with exposure to passive smoking in childhood (1); how passive smoking in childhood enhances the effects of active smoking as an adult on risk for RA (2); and how the combination of childhood passive smoking and active smoking in adulthood contributes to the development of seropositive RA (3).

passive exposure to tobacco smoke during childhood was not increased in individuals who did not smoke at all as adults, and it only acted as an accelerating factor in adult smokers. This new knowledge thus provides an additional argument to abstain from smoking as an adult for those individuals who were exposed to tobacco smoke as children.

Overall, the study by Yoshida et al.[6] provides new interesting and important information on the effects of smoking on the risk of developing seropositive RA and also illustrates how a longitudinal and carefully performed study such as the Nurses' Health Study can be used to decipher the effects of lifestyle — and in the future, probably also molecular events – during the entire lifespan and how events in childhood can influence the effects of lifestyle choices on health during adulthood (FIG. 1).

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1. Catrina, A. I. et al. Mechanisms leading from systemic autoimmunity to joint-specific disease in rheumatoid arthritis. *Nat. Rev. Rheumatol.* **13**, 79–86 (2017).
2. Deane, K. D. et al. Genetic and environmental risk factors for rheumatoid arthritis. *Best Pract. Res. Clin. Rheumatol.* **31**, 3–18 (2017).
3. Sparks, J. A. et al. Genetics, environment, and gene-environment interactions in the development of systemic rheumatic diseases. *Rheum. Dis. Clin. North Am.* **40**, 637–657 (2014).
4. Seror, R. et al. Passive smoking in childhood increases the risk of developing rheumatoid arthritis. *Rheumatology* **58**, 1154–1162 (2019).
5. Hedström, A. K. et al. Exposure to passive smoking and rheumatoid arthritis risk: results from the Swedish EIRA study. *Ann. Rheum. Dis.* **77**, 970–972 (2018).
6. Yoshida, K. et al. passive smoking throughout the life course and the risk of incident rheumatoid arthritis in adulthood among women. *Arthritis Rheumatol.* https://doi.org/10.1002/art.41939 (2021).
7. Carlens, C. et al. Perinatal characteristics, early life infections and later risk of rheumatoid arthritis and juvenile idiopathic arthritis. *Ann. Rheum. Dis.* **68**, 1159–1164 (2009).
8. Mandl, L. A. et al. Is birthweight associated with risk of rheumatoid arthritis? Data from a large cohort study. *Ann. Rheum. Dis.* **68**, 514–518 (2009).
9. Klareskog, L. et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum.* **54**, 38–46 (2006).

Competing interests

The author declares no competing interests.

Differentiating between UCTD and early-stage SLE: from definitions to clinical approach

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Abstract | Systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous clinical manifestations that can potentially affect every organ and system. SLE is usually identified on the basis of clinical or serological manifestations; however, some individuals can present with signs and symptoms that are consistent with SLE but are not sufficient for a definite diagnosis. Disease in these individuals can either progress over time to definite SLE or remain stable, in which case their disease is often described as intermediate, possible or probable SLE. Alternatively, such individuals might have undifferentiated connective tissue disease (UCTD). Being able to differentiate between those with stable UCTD and those with SLE at an early stage is important to avoid irreversible target-organ damage from occurring. This Review provides insight into existing and evolving perceptions of the early stages of SLE, including clinical and mechanistic considerations, as well as potential paths towards early identification and intervention. Further research into the earliest phases of SLE will be important for the development of targeted diagnostic approaches and biomarkers for the identification of individuals with early disease who are likely to progress to definite SLE.

Systemic lupus erythematosus (SLE) is an autoimmune disease in which immune deregulation leads to autoantibody production, causing heterogeneous clinical manifestations that can potentially affect every organ and system. The development of clinically defined SLE can be preceded by several years by the onset of immune abnormalities and clinical features that fall below the threshold required for a definite diagnosis[1]. In fact, although some patients are diagnosed with SLE at initial presentation, a non-negligible number of patients present with some manifestations that are indicative of SLE but are not sufficient for a definite diagnosis[2]. These patients can either progress to a definite diagnosis of SLE as new disease manifestations develop over time, or follow a limited but stable disease course that, even after many years, does not meet the requirements for a diagnosis of SLE. Several terms, including latent, intermediate, probable and possible SLE, have been used to describe disease in individuals who cannot be diagnosed with definite SLE, and attempts have been made to define their diverse clinical presentations. However, these descriptive terms are not necessarily mutually exclusive and probably refer to a mix of patients at different phases of disease development. Moreover, in clinical practice it is not uncommon to find individuals with clinical and serological features that might be indicative of an autoimmune disorder but without findings that are specific for a defined connective tissue disease (CTD); these individuals might fall within the spectrum of undifferentiated connective tissue disease (UCTD). Distinguishing between UCTD and the early stages of SLE can be challenging, as these conditions can share similar clinical characteristics that are suggestive of SLE, yet are not sufficient for a definite diagnosis (BOX 1).

Borrowing from work carried out in rheumatoid arthritis (RA), a natural history timeline has been proposed that reflects the evolution of SLE[3]. In such a paradigm, the spectrum of SLE can be imagined along a continuum (FIG. 1). Before SLE develops, individuals are 'at-risk' of SLE. A growing number of genetic and environmental risk factors have been associated with SLE, such as complement gene variants[4], HLA haplotypes[5] and viral infections[6]. Identifying individuals at a high risk of developing SLE could potentially enable disease prevention interventions. Moving along the continuum, some individuals will develop asymptomatic preclinical autoimmunity. This group is characterized by the presence of serological activity consistent with a diagnosis of SLE, such as antinuclear antibody (ANA)

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Key points

- Systemic lupus erythematosus (SLE) is a complex autoimmune condition characterized by autoantibody production that can precede disease by several years and heterogeneous clinical manifestations.
- A considerable proportion of individuals have clinical and serological features that are suggestive of a systemic autoimmune disorder, but cannot be diagnosed as having a defined connective tissue disease.
- Nomenclature used to define such individuals has been inconsistent, with terms such as latent, incomplete, possible and probable SLE being used, as well as undifferentiated connective tissue disease (UCTD).
- Although discriminating between UCTD and early SLE can be challenging, the presence of some features (such as a malar rash or specific autoantibodies) would tip the diagnosis in favour of SLE.
- The absence of new clinical and laboratory manifestations over a 3-year period and the lack of a connective tissue disease-specific serological profile could support a diagnosis of UCTD.
- The specificity of definitions of SLE-spectrum disorders should improve in the future as more molecular data become available with which disease subgroups can be defined.

positivity or positivity for sub-serologies such as anti-double-stranded DNA (dsDNA) antibodies or anti-Sm antibodies, but has no overt clinical signs or symptoms of the disease. Further along the continuum, individuals with serological activity might develop initial clinical features of autoimmune disease that are not enough for a diagnosis of a defined CTD; such individuals might have UCTD. Eventually, patients might develop full-blown disease with clinical and serological manifestations that allow a diagnosis of SLE. Thus, during the natural history of the disease, there is a phase in which it is difficult to predict future outcomes. Will the disease remain stable, or will it evolve into full-blown SLE? Does the patient have SLE at an early stage or UCTD?

In this Review, we explore the current understanding of UCTD and early-stage SLE and potential paths for the early identification of SLE, including clinical and pathogenic considerations that could aid clinicians when managing patients with these conditions. We also provide some general comments on the management of UCTD, including pregnancy planning, and on future research directions that could aid the early identification of SLE and prevent irreversible target-organ damage from occurring.

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UCTD or early-stage SLE?

The term UCTD refers to a group of autoimmune disorders that present with clinical and immunological manifestations that do not fulfil any of the existing diagnostic or classification criteria for a defined CTD. At disease onset, a sizeable proportion of patients — up to 50% in some cohort studies — might fall into the category of having unclassifiable disease[7]. An important point to bear in mind when discussing UCTD and SLE is that classification and diagnosis are two different entities. Classification criteria are formed on the basis of standardized definitions of a condition and are mainly used to create a uniform group of patients for clinical research; several sets of classification criteria have been developed over the years to help researchers to identify homogeneous cohorts of patients with SLE[8–10]. Conversely, diagnostic criteria are absent for SLE and UCTD, and the diagnostic process relies on physicians recognizing collections of signs and symptoms. Therefore, although most of the ambiguity in the available literature is due to the absence of updated classification criteria, in clinical practice, discrimination between UCTD and early stages of SLE ultimately relies on the physician's judgement.

During the disease course, some patients with UCTD will go on to develop a defined disease such as SLE, systemic sclerosis (SSc), Sjögren syndrome, dermatomyositis, polymyositis, mixed connective tissue disease or RA[11–13]. The most common manifestation in patients with UCTD is arthritis, which is present in up to 60% of patients[14–16]. Cutaneous manifestations, particularly photosensitivity, are common in both UCTD and early-stage SLE; however, some clinical manifestations, such as malar rash, discoid rash or chronic cutaneous lupus, would support a diagnosis of SLE rather than UCTD. Haematological disorders such as leukopenia and thrombocytopenia can also be found in about half of patients with UCTD[14–16]. By contrast, severe SLE manifestations such as renal disease, neurological involvement or haemolytic anaemia are unusual in UCTD[14–16].

Over the past few years, the understanding of UCTD has progressed. A 'UCTD concept' has been emphasized that goes beyond classification criteria[17], moving from referring to patients with non-specific features to a distinct disease phenotype that is different from the full-blown CTDs[2]. Follow-up studies of various UCTD cohorts have clearly shown that many patients with UCTD will not develop additional clinical and/or serological abnormalities during the follow-up period (known as stable UCTD). The number of patients with stable UCTD varies between studies but could be up to 60% of patients[11–13]. Stable UCTD is usually characterized by a limited number of manifestations, the absence of severe organ involvement and, usually, positivity for fewer autoantibody subtypes compared with SLE. Unlike stable UCTD, early or evolving UCTD refers to initial disease presentations that are more prone to developing into a definite CTD within a short period of time, although, in some cases, this can happen over a few years following the onset of symptoms[13]. Some scenarios in the follow-up of all patients with UCTD require specific attention, including surgery, vaccination, changes in treatment and concomitant infections. Similarly, particular attention

Box 1 | **UCTD or early SLE?**

Differentiating between undifferentiated connective tissue disease (UCTD) and the early stages of systemic lupus erythematosus (SLE) can present a challenge for the physician. Take a 22-year-old woman presenting with positive test results for antinuclear antibodies and anti-SSA/Ro antibodies, oral aphthosis and arthritis as an example. The absence of signs or symptoms with high specificity for a definite connective tissue disease would support the diagnosis of UCTD; however, there is a chance that a treating clinician might consider this patient to have incomplete or early-stage SLE. Conversely, if a patient with a similar clinical profile presented with a positive test result for anti-double-stranded DNA antibodies, the diagnosis would tip in favour of SLE. The time between the onset of signs or symptoms and the moment of diagnosis is critical when distinguishing between these conditions and is important when planning follow-up, as the long-term outcomes and prognosis differ between these diseases.

should be given to pregnancy counselling and management, which requires a multidisciplinary approach to improve maternal and fetal outcomes (BOX 2).

Clearly, being able to differentiate stable UCTD from the early stages of a defined CTD could have implications for therapy and prognosis; both clinical and serological variables should be used to support the treating physician when identifying which patients are most likely to maintain stable UCTD. Moreover, increasing evidence has shown that 'early' or 'incomplete' SLE (terms used to identify patients with clinical features and/or serological abnormalities suggestive of SLE[18]) is not necessarily a benign form of the disease[19]. Such observations are of great importance and should inspire physicians to identify patients in a timely manner, potentially leading to earlier implementation of management strategies that could lead to an improved prognosis.

How many patients are in the grey area? Although patients with features of autoimmunity that cannot be classified as any specific CTD seem to be relatively common in clinical practice, consistent epidemiological data on UCTD and early-stage SLE are scarce. This lack of solid evidence might be explained by the fact that different selection criteria have been used to define these conditions around the world. Factors such as age, sex, ethnicity, access to care, socio-economic status, geographic region, national origin and environmental exposure could also have a role in the heterogeneity of the reported data.

The nomenclature used in the literature to refer to patients with clinical and laboratory features suggestive of SLE but not sufficient for definite classification is heterogeneous; therefore, in this Review the nomenclature that is used when referring to specific studies and cohorts is based on the inclusion criteria or definition used in each study. However, a note of caution is warranted about the analysis of the available literature. It was beyond the scope of this narrative review to perform a systematic search of the literature for the definitions that have been used over the years for incomplete SLE, UCTD or early-stage CTD; thus, despite the use of different nomenclature, the patients included in the analysed studies might actually have similar or overlapping characteristics. Available data are summarized in TABLE 1. To improve comparability, studies using similar inclusion criteria have been grouped together.

The studies in TABLE 1 report highly heterogeneous rates of disease progression towards SLE that range from 2.9% to as high as 57.0% over a period of 1–3 years[15,20,21]. The length of follow-up in these studies ranged from 1 to 14 years, and the number of patients enrolled from 22 to 665. Single-centre data from the rheumatology unit at the University of Pisa in Italy show that 20% of newly referred patients presented with a CTD (excluding RA) and that about 13% of these patients had a diagnosis of UCTD[11,22]. Age at onset and diagnosis in patients with UCTD have been investigated in data from the RELESSER registry, which reveal that patients with UCTD experience their first symptoms at an older age than patients with definite SLE (41.0 versus 32.6 years)[23]. Patients with UCTD were also typically older when the diagnosis was first made (42.9 versus 34.6 years)[23]. Therefore, the age at onset of symptoms should be considered when differentiating between UCTD and early-stage SLE. A study of 3,397 patients from the Lupus Family Registry and Repository[24] who fulfilled the 1997 ACR SLE classification criteria[25] and 291 patients with what the authors of the study defined as incomplete SLE (individuals who met three ACR criteria and did not meet the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE[26]), found both groups of patients to be predominantly female (nearly 90%)[27]. However, patients with incomplete SLE were, on average, older at diagnosis than patients with SLE who fulfilled both sets of criteria (47.5 versus 42.0 years). Furthermore, the percentage of individuals from an African American or Latin American background was lower among those with incomplete SLE than among those with SLE (23.7% versus 32.6% and 4.1% versus 7.2%, respectively), whereas the opposite was true for individuals with a European American background (56.7% versus 44.3%)[27].

What can be learned from available epidemiological data? The studies in TABLE 1 support the perception of treating physicians that UCTD and early-stage SLE represent a considerable proportion of patients attending rheumatology clinics. However, a precise estimation of the incidence and prevalence of incomplete SLE, early-stage SLE and UCTD is still strongly limited by the diagnostic overlap among these conditions. When pooling the information from prospective studies, it is clear that the time between the onset of symptoms or signs and the moment of the diagnosis represents an important variable. In fact, when comparing the progression of patients who have been followed prospectively over several years, individuals with UCTD presented a lower rate of yearly progression to a CTD (range of 2.9–13.2% in the studies included in TABLE 1) compared with those identified as having incomplete SLE (range of 3.0–57.0%). This observation further supports the proposed clinical distinction between UCTD and early-stage SLE beyond the pure semantic choice. From a practical point of view, the absence of new clinical and laboratory manifestations over a 3-year period and the lack of a CTD-specific serological profile (such as anti-dsDNA or anti-Sm antibodies) could support a diagnosis of UCTD.

The role of clinical manifestations. As previously stated, the clinical and laboratory characteristics of patients with suspected early-stage SLE, incomplete SLE and

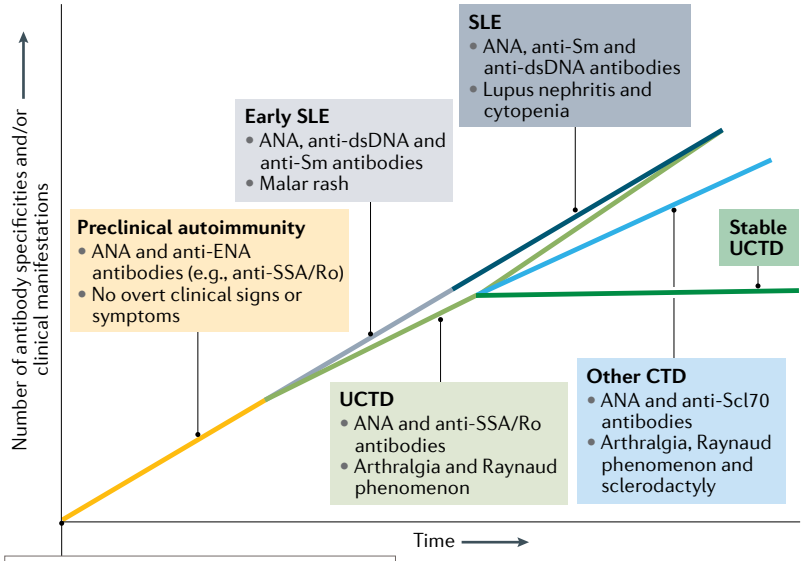

Fig. 1 | **Natural history timeline of the evolution of SLE.** The spectrum of systemic lupus erythematosus (SLE) can be imagined along a continuum. Some individuals might be considered 'at-risk' of developing a connective tissue disease (CTD) because of genetic and environmental risk factors. Before SLE clinically develops (preclinical autoimmunity), individuals might present with a positive antinuclear antibody (ANA) test and with positivity for an anti-extractable nuclear antigen (ENA) antibody (such as anti-SSA/Ro antibodies), but with no overt clinical signs or symptoms. Further along the continuum, individuals with serological activity might have some clinical features of a CTD (such as arthralgia, Raynaud phenomenon or sicca symptoms) but not enough to be diagnosed with a defined CTD. These individuals might be defined as having undifferentiated connective tissue disease (UCTD) and can either stay clinically and serologically stable over time (stable UCTD) or go on to develop a defined CTD. Some sub-serological profiles (such as anti-double-stranded DNA (dsDNA) antibodies or anti-Sm antibodies) are suggestive of a diagnosis of SLE. In individuals who are positive for these autoantibodies, those who present with mild clinical profiles (such as a malar rash but no other signs or symptoms of SLE) could be considered as having early SLE, whereas those who develop multiple organ involvement (such as lupus nephritis, serositis or neuropsychiatric features), would be considered to have definite SLE.

UCTD might overlap, particularly when these conditions are first diagnosed. Overall, patients with UCTD seem to present with milder disease manifestations than those with incomplete SLE. For example, disease activity was moderate to severe in nearly one-third of individuals with incomplete SLE (defined as fulfilling one to three of the 1997 ACR classification criteria for SLE) included in the Peking Union Medical College Hospital Registry[28]. Furthermore, more than half of all patients with incomplete SLE had organ damage according to the SLICC–ACR Damage Index. Some clinical manifestations were observed more frequently in the patients with incomplete SLE than would be expected to occur in patients with UCTD, of which the pulmonary domain was the most common SLICC–ACR Damage Index domain, reported in 22.1% of patients, followed by the renal domain in 11.7% and the neurological domain in 10.4%[28]. Hypertension, cardiovascular events and severe infections were reported less often in patients with incomplete SLE than in those with definite SLE[27]. These results are concordant with the lower rates of hospitalization and death observed in individuals with incomplete SLE compared with those with SLE in the RELESSER registry[23].

When analysing studies reporting the rate of progression from UCTD to a definite CTD, some considerations are worth noting. First, some studies enrol patients with SLE-specific findings, such as being positive for anti-dsDNA antibodies or having distinct skin rashes, as having UCTD. Second, the UCTD concept is a relatively recent insight that was not completely elucidated when some older studies were published. Both of these factors will have implications for the interpretation of results. In addition, socio-epidemiological factors such as access to health care can influence the progression and prognosis of CTDs. For example, in data from the UK Clinical Practice Research Datalink, in the 5 years preceding a diagnosis of SLE the median general practitioner consultation rate per year was 9.2 for patients with SLE compared with 3.8 for matched individuals without SLE[29]. Therefore, some intrinsic biases in the available evidence might be at least partially explained by the heterogeneous access to rheumatology clinics around the world.

Nevertheless, although contrasting results have been reported among the various cohorts[7,15,20,21,30], some prognostic factors can be identified for progression to definite CTDs that can help treating physicians when disease progression is a matter of concern. Among these factors, the type and timing of the clinical manifestations require some consideration. In a prospective study of patients at risk of developing autoimmune CTDs (defined as positive for ANA, ≤1 SLICC clinical criterion and symptom duration of <12 months), the presence of ultrasound-detectable synovitis at baseline seemed to be more common among those who progressed to autoimmune CTDs than among those who did not[21]. In fact, the presence of some symptoms is particularly suggestive of a definite CTD (such as puffy fingers, Gottron's papules, anti-Sm antibodies and nephritis) and should rule out a diagnosis of UCTD. The timing of the presentation of symptoms also needs to be considered. Among patients with UCTD who progress to a CTD, SLE is the most frequently reported diagnosis (20–60%)[15,17,19,31]. This progression often occurs within the first 5 years following the onset of the first clinical features, although a later progression has also been reported[32]. In addition, patients who eventually develop SLE accrue clinical manifestations over a period of months to years; the proportion of individuals with manifestations in three or more British Isles Lupus Assessment Group index domains increased from 18.7% at 5 years before diagnosis to 39.7% in the year before the diagnosis of SLE was made[33].

In this Review, we do not aim to provide new classification criteria for UCTD. Nevertheless, to support physicians from a practical point of view, a couple of considerations are important to note. First, owing to their low specificity for definite CTDs, some symptoms and signs (such as isolated xerostomia or xerophthalmia) might not be enough to support a clinical diagnosis of UCTD even when accompanied by a positive

ANA test. This suggestion is in line with the fact that sicca syndrome might not represent a definite autoimmune entity[34]. Second, in 2015 a joint task force between the European Respiratory Society and the American Thoracic Society proposed a set of classification criteria for a new entity called interstitial pneumonia with autoimmune features to improve the identification of individuals who have interstitial lung disease and features of autoimmunity, without having a definite CTD[35]. Differentiating CTD-associated interstitial lung disease (including interstitial pneumonia with autoimmune features) from idiopathic pulmonary fibrosis is of critical importance, as CTD-associated interstitial lung disease generally has a better prognosis, and the therapeutic approaches differ substantially between the two forms[36]. Overall, although a definite diagnosis of SLE should apply to patients with a clinical presentation that includes the involvement of renal, neurological or cardiovascular systems, differentiating between UCTD and early-stage SLE on the sole basis of clinical presentation can be difficult.

The role of the laboratory and autoantibody testing. One of the main challenges in the diagnosis of CTDs is the fact that characteristic serological abnormalities (such as ANA and rheumatoid factor) are shared by several diseases, although some antibody specificities do have diagnostic value in terms of specificity for defined CTDs, such as anti-centromere antibodies for limited cutaneous SSc and anti-topoisomerase-I antibodies for diffuse cutaneous SSc[2], or anti-Sm and anti-dsDNA antibodies for SLE[37]. Similarly, in addition to the type of antibody specificities that are detectable in a patient, the cumulative number of autoantibodies for which a patient tests positive can be an indicator of progression towards a definite diagnosis of SLE[38]. In fact, patients with SLE develop a mean of 0.3 new autoantibody specificities per year and test positive for a mean of 3 autoantibody specificities at the time of diagnosis[39]. Nevertheless, a need remains to identify meaningful preclinical biomarkers to identify patients with suspected CTDs[21,40].

In a study involving 148 patients with UCTD who tested positive for anti-SSA/Ro antibodies, 24% went on to develop a defined CTD within 4.5 years, mainly SLE and primary Sjögren syndrome[41]. In another study of 70 patients with UCTD, those with only anti-SSA/Ro antibodies that recognize the 60-kDa antigen were more likely to go on to develop SLE, whereas those with both anti-SSA/Ro antibodies that recognize the 52-kDa antigen and those that recognize the 60-kDa antigens were more likely to develop primary Sjögren syndrome[42]. In line with this finding, in a retrospective study that included 97 individuals who were positive only for autoantibodies that recognize the 52-kDa Ro antigen ($Ro52^+Ro60^-$) and 100 individuals who were $Ro52^+Ro60^+$, more than 70% of $Ro52^+Ro60^-$ individuals were diagnosed with a CTD, the most prevalent of which were UCTD (14%), RA (13%), SLE (10%) and Sjögren syndrome (10%), and 23 $Ro52^+Ro60^-$individuals (24%) did not receive a CTD diagnosis[43]. By contrast, 87% of $Ro52^+Ro60^+$ individuals were diagnosed as having a CTD, including Sjögren syndrome (34%), SLE (23%) and UCTD (12%)[43]. In a study from the USA that involved 213 patients who had shown symptoms of early-stage UCTD for at least 1 year, the development of SLE after 5 years was associated with specific demographic features (such as African American ethnicity and younger age), clinical symptoms (such as pleuritis and/or pericarditis, alopecia and discoid lesions) and laboratory abnormalities (including a homogeneous ANA pattern, anti-dsDNA and anti-Sm antibodies, positive Coombs' test and false-positive test for syphilis)[44]. Among the laboratory parameters, the strongest association with SLE was found with a homogeneous ANA pattern and anti-Sm antibodies. Furthermore, a study of 130 patients with SLE showed that 18.5% of patients tested positive for either IgG or IgM anticardiolipin (aCL) antibodies before a definite diagnosis with SLE was made, providing evidence that aCL antibodies can be detected up to 7.6 years (mean average 3 years) before SLE onset[45]. A positive test for aCL antibodies was also associated with a worse prognosis, as it was associated with an increased prevalence of neurological, renal and haematological complications, as well as with an increased risk of thrombotic events.

Autoantibodies are not only part of the classification process for CTDs, but also have an important role as biomarkers for predicting complications and/or comorbidities. In clinical practice, patients often present with a positive ANA test, which is not specific to any particular CTD, but with no extractable nuclear antigen profiling, thereby limiting the possibility of predicting the disease course. Being able to identify those patients with UCTD who are at a higher risk of developing severe disease manifestations or organ damage on the basis of autoantibody specificity would enable physicians to plan tailored management and follow-up of these patients. Autoantibody profiling would be especially critical for guiding the management of patients

Box 2 | **Pregnancy and counselling in UCTD**

Undifferentiated connective tissue disease (UCTD) seems to be one of the most common rheumatic diseases in women of childbearing age, with one study suggesting that the prevalence of undiagnosed UCTD among pregnant women could be as high as 2.5%[97]. Several studies have reported an increased prevalence of adverse pregnancy outcomes in women with UCTD compared with the general population of up to 25–30% of all pregnancies[14,98–102]. However, to date, no clear international recommendations exist for the management of UCTD, and many patients diagnosed with UCTD might not receive specialized counselling when planning or during pregnancy. Importantly, UCTD is reported to be the most common diagnosis in the Italian Registry on Immune-Mediated Complete Heart Block[103]. Rationally, extractable nuclear antigen profiling should therefore be mandatory before pregnancy in patients with UCTD because of the possibility of developing fetal complete heart block, as well as of developing other complications such as neonatal cutaneous lupus, which is associated with the presence of maternal anti-SSA/Ro antibodies[104]. Furthermore, when planning a pregnancy with a patient with UCTD, the presence of antiphospholipid antibodies (aPLs) should be assessed. Although the precise prevalence of aPLs in patients with UCTD is still unclear, their presence is strongly associated with poor pregnancy outcomes, including preeclampsia, premature birth, intrauterine growth restriction and intrauterine death[105]. While the field awaits the creation of specific guidelines for UCTD, pregnancy counselling and management in women with UCTD should follow the same recommendations as those for patients with SLE[106]. When planning a pregnancy, women with UCTD should always be tested for aPLs and antibodies that recognize extractable nuclear antigens and referred to a specialist.

Table 1 | **Rate of development from UCTD or early-stage SLE to definite SLE**

Study (year)	Country or region	Diagnosis[a]	Study entry criteria	Average no. years follow-up	No. patients	No. patients who develop SLE	Percentage who develop SLE	Ref.
Incomplete SLE								
Greer & Panush (1989)	USA	Incomplete SLE	Fewer than 4 criteria from the 1982 ACR SLE classification criteria	1.6	38	2	5.3	82
Swaak et al. (2001)	Europe	Incomplete SLE	Symptoms related to one organ system plus the presence of ANA	3.0	100	3	3.0	83
Stahl Hallengren et al. (2004)	Sweden	Incomplete SLE	Fewer than 4 criteria from the 1982 ACR SLE classification criteria	13.0	28	16	57.0	20
Laustrup et al. (2010)	Denmark	Incomplete SLE	Fewer than 4 criteria from the 1982 ACR SLE classification criteria	8.0	37	7	19.0	84
Olsen et al. (2012)	USA	Incomplete SLE	Fewer than 4 criteria from the 1997 ACR SLE classification criteria	3.8	22	3	14.0	85
UCTD								
Calvo-Alen et al. (1996)	USA	UCTD	Fewer than 4 criteria from the 1982 ACR SLE classification criteria	5.0	143	18	12.6	86
Mosca et al. (1998)	Italy	UCTD	Clinical manifestations suggestive of a CTD plus at least one non-organ-specific autoantibody	3.0	91	12	13.2	22
Danieli et al. (1998)	Italy	UCTD	Symptoms of a CTD but do not fulfil criteria for any specific CTD	5.0	84	7	8.3	87
Danieli et al. (1999)	Italy	UCTD	At least 2 signs from a defined list of criteria and do not fulfil criteria for any specific CTD	5.0	165	5	7.4	88
Williams et al. (1999)	USA	UCTD	Fewer than 4 criteria from the 1982 ACR SLE classification criteria	10.0	115	11	9.6	89
Cavazzana et al. (2001)	Italy	UCTD	Anti-SSA/Ro antibody positivity plus clinical or serological abnormalities not sufficient for diagnosis as a CTD	4.5	148	11	7.4	41
Bodolay et al. (2003)	Hungary	UCTD	Clinical manifestations suggestive of a CTD plus at least one non-organ-specific autoantibody	5.0	665	28	4.2	90
Guerrero et al. (2013)	Colombia	UCTD	Clinical manifestations suggestive of a CTD, ANA positive and do not fulfil criteria for any specific CTD	4.3	94	8	8.5	91
Garcia-González et al. (2017)	Spain	UCTD	Fewer than 4 criteria from the 1997 ACR SLE classification criteria	11.0	98	9	9.2	30
Bortoluzzi et al. (2017)	Italy	UCTD	Clinical manifestations suggestive of a CTD plus at least one non-organ-specific autoantibody	3.0	206	6 (1997 ACR)	2.9	15
				14.0		8 (2012 SLICC)	3.9	
Zucchi et al. (2020)	Italy	UCTD	Pregnant women; clinical manifestations suggestive of a CTD, ANA positive and do not fulfil criteria for any specific CTD	4.7	81	3[b]	3.7	92
Other								
Ganczarczyk et al. (1989)	Canada	Latent lupus	Features suggestive of SLE but do not meet the 1982 ACR classification criteria	8.0	22	7	31.8	93
Al Daabil et al. (2014)	USA	Potential SLE	Fewer than 4 criteria from the 1997 ACR SLE classification criteria	6.3	264	56	21.2	94
Tiao et al. (2016)	USA	Sub-acute CLE	Clinician diagnosis of sub-acute CLE	3.8	85	30 (1997 ACR)	35.3	95
						34 (2012 SLICC)	40.0	
Yusof et al. (2018)	UK	At-risk of autoimmune CTD	ANA positive, one or fewer criteria from the 2012 SLICC SLE classification criteria and do not fulfil criteria for any other specific CTD	1.0	118	14	11.9	21
Ramsey-Goldman et al. (2019)	USA	Probable SLE	Three criteria from the 1997 ACR SLE classification criteria	0.0 (baseline)	92	35 (2012 SLICC)	38.0	96
			Three criteria from the 1997 ACR SLE classification criteria and do not fulfil the 2012 SLICC criteria	1.5	43	6 (2012 SLICC)	14.0	

Studies included in this table were mostly longitudinal studies with at least 20 patients. ANA, antinuclear antibody; CLE, cutaneous lupus erythematosus; CTD, connective tissue disease; SLE, systemic lupus erythematosus; SLICC, systemic lupus international collaborating clinics; UCTD, undifferentiated connective tissue disease. [a]Patients with clinical and serological manifestations suggestive of SLE but not enough for classification as such. [b]Developed during pregnancy.

previously identified as having UCTD, in whom the detection of additional specific autoantibodies should not only increase the probability of disease progression, but also suggest a prompt approach to investigation and therapy[35,37,46–48]. For example, close monitoring of renal function and urine analysis should be carried out in patients with UCTD in whom anti-dsDNA or anti-Sm antibodies are detected, whereas cardiopulmonary testing and malignancy screening should be performed in patients with UCTD in whom an autoantibody profile suggestive of SSc is detected.

The role of classification criteria. Over the past few years, a growing body of evidence has accelerated the prompt diagnosis and classification of CTDs, and new classification criteria have been developed for many diseases. In 2010, a new set of classification criteria for RA was presented in an attempt to capture the early stages of RA[49,50]. Studies have shown that, when applying the new criteria, the prevalence of undifferentiated arthritis was reduced compared with estimates that used the 1987 ACR classification criteria for RA[49,50]. A step towards the very early diagnosis of SSc has also been made, with the identification of three red flags, namely Raynaud phenomenon, puffy fingers and a positive ANA test[51]. The importance of early classification has also emerged in SLE. The 2012 SLICC classification criteria for SLE were designed to be more clinically effective than the 1997 ACR classification criteria for SLE, thereby enabling the inclusion of more patients with clinically defined SLE in research studies than would be possible using the ACR criteria[26]. None of the available sets of classification criteria was specifically designed to address the topic of differentiating UCTD from SLE (early or definite); however, the accuracy of both the 1997 ACR and the 2012 SLICC criteria have been tested in patients with UCTD from selected cohorts around the world (TABLES 2 and 3, respectively).

Although the number of the studies is limited, affecting the possibility of comparing data across studies with different designs and inclusion criteria, some findings are worth noting. Skin and joint involvement are the most common clinical manifestations from both the 1997 ACR and 2012 SLICC classification criteria sets that are reported in patients with incomplete SLE or UCTD (TABLES 2 and 3), whereas kidney and central nervous system involvement are less commonly reported. This latter finding does not come as a surprise, as those manifestations would be more likely to support a diagnosis of definite SLE than skin or joint manifestations. Interestingly, although haematological involvement seems to be common (particularly leukopenia or lymphopenia), thrombocytopenia is relatively less common in these patients. No major differences are evident when comparing studies using the 1997 ACR or 2012 SLICC classification criteria. However, in a cohort of 133 women with UCTD who were not classifiable as having SLE by either the 1997 ACR or 2012 SLICC classification criteria, 17% were classifiable as having SLE when the recently developed 2019 EULAR–ACR classification criteria for SLE were applied[19]. These observations further support the concept that although classification criteria are needed for research purposes, in clinical practice the identification of some features (such as anti-dsDNA or anti-Sm antibodies or a malar rash) should leverage the diagnosis in favour of SLE.

From the laboratory perspective, a positive test for anti-dsDNA antibodies was reported in up to 100% of patients in studies using the 1997 ACR criteria (TABLE 2) and in up to 46% of patients in studies using the 2012 SLICC criteria (TABLE 3). This aspect is crucial: can we ever say that a patient who tests positive for anti-dsDNA antibodies has UCTD? Or should the presence of anti-dsDNA antibodies rule out a diagnosis of UCTD in favour of a diagnosis of early-stage SLE or SLE? Although the specificity of anti-dsDNA (and of anti-Sm) antibodies for SLE is undoubted, at present, the diagnostic decision relies purely on clinical judgment. As the presence of any manifestation specific for SLE could support a diagnosis of the definite CTD, discriminating between full-blown SLE and early-stage SLE will need to rely on both the clinical manifestation and the timing between the onset of signs and symptoms and the moment of diagnosis.

Overall, although some differences still exist among studies, the available literature seems to converge on the following definitions. UCTD is usually defined by the presence of signs and symptoms suggestive of a CTD but not fulfilling the criteria for any defined CTDs; a positive ANA test; and a disease duration of at least 1 year. Studies that include patients with incomplete SLE usually refer to individuals who meet fewer than four ACR criteria items for SLE. The definition of early SLE is the most heterogeneous, and a solid consensus does not yet exist. Available studies[32,52] that use this definition usually refer to a diagnosis made by an experienced rheumatologist on the basis of clinical experience and judgement. The current challenge is to translate the definitions used in research studies (most of which refer to classification criteria) into clinical practice. To provide some clinical guidance, we have suggested some preferred nomenclature for SLE spectrum disorders and UCTD in TABLE 4.

Can we prevent progression to SLE?

It is not yet understood which patients presenting with UCTD will develop SLE during the following years; however, on the basis of the data discussed in previous sections, patients who are at risk of progressing to SLE can be identified. Similarly, it is not fully known whether and which therapeutic interventions might prevent or delay the development of a definite rheumatic disease. As such, the management of patients with disease that cannot be classified as a CTD should be individually tailored and steered by the patients' clinical manifestations. For example, patients with features suggestive of SLE should be closely monitored by regular blood and urine testing, along with clinical examination, to be sure that signs of life-threatening manifestations such as kidney involvement are detected as early as possible[53,54]. By contrast, surveillance of patients with manifestations and/or autoantibody profiles suggestive of SSc should include echocardiography because these patients are at an increased risk of developing pulmonary arterial hypertension[55].

No randomized controlled trials of management strategies have ever been conducted for UCTD, mainly

Table 2 | **1997 ACR SLE classification criteria fulfilment in patients with early-stage SLE or UCTD**

Characteristic	Al Daabil et al. (2014)[94]	Swaak et al. (2001)[83]	Rua-Figueroa et al. (2015)[23]	Chen et al. (2015)[28]	Mosca et al. (2019)[32]	Laustrup et al. (2009)[84]	Vaz et al. (2009)[16]	Tiao et al. (2016)[95]	Overall range (%)
Demographics									
Number of patients	161	100	345	77	389	26	74	30	NA
Diagnosis	Potential SLE	Incomplete SLE	Incomplete SLE	Incomplete lupus syndromes	Early SLE	Incomplete SLE	Lupus-like UCTD	Sub-acute CLE with SLE	NA
Clinical criteria (%)									
Malar rash	11.0	4.0	11.0	9.1	49.6	19.2	13.0	43.3	4.0–49.6
Discoid rash	1.0	4.0	7.1	0.0	9.3	3.8	NR	NR	0.0–9.3
Photosensitivity	22.0	NR	20.5	1.3	31.6	46.1	25.0	96.7	1.3–96.7
Oral ulcers	11.0	NR	7.3	7.8	21.6	7.7	22.0	60.0	7.3–60.0
Arthritis	57.0	15.0	44.2	20.8	57.6	30.7	49.0	60.0	15.0–60.0
Serositis (pleuritis/ pericarditis)	13.0	NR (NR/4.0)	8.8	20.8	NR (22.4/18.8)	19.2	4.0	3.3	4.0–20.8
Renal disorder	1.0	NR	4.3	16.9	13.1	15.3	NR	19.2	1.0–19.2
Persistent proteinuria	NR	4.0	NR	NR	NR	NR	NR	NR	NA
Cellular cast	NR	3.0	NR	NR	NR	NR	NR	NR	NA
Neurological disorder	4.0	NR	1.2	6.5	NR	4.0	NR	6.7	1.2–6.7
Seizures	NR	1.0	NR	NR	2.8	NR	NR	NR	1.0–2.8
Psychosis	NR	0.0	NR	NR	1.0	NR	NR	NR	0.0–1.0
Haematological disorder	30.0	NR	43.5	51.9	NR	30.7	NR	50.0	30.0–51.9
Haemolytic anaemia	NR	2.0	NR	NR	4.6	NR	NR	NR	2.0–4.6
Leukopenia	NR	36.0	NR	NR	16.2	NR	28.0	43.3	16.2–36.0
Thrombocytopenia	NR	8.0	NR	NR	6.6	NR	14.0	16.7	6.6–16.7
Immunological criteria (%)									
Anti-dsDNA antibodies	16.0	NR	NR	22.1	71.7	100.0	29.0	50.0	16.0–100.0
Anti-Sm antibodies	3.0	NR	NR	5.2	30.2	NR	4.0	35.7	3.0–35.7
aCL antibodies	14.0	NR	NR	NR	18.1	NR	NR	37.5	14.0–37.5
LA	4.0	NR	NR	NR	15.1	NR	NR	33.3	4.0–33.3
ANA	98.0	100.0	94.7	97.4	99.5	100	100.0	96.6	94.7–100.0

Studies included in this table were mostly longitudinal studies with at least 20 patients. aCL, anticardiolipin; ANA, antinuclear antibody; CLE, cutaneous lupus erythematosus; dsDNA, double-stranded DNA; LA, lupus anticoagulant; NA, not applicable; NR, not reported; SLE, systemic lupus erythematosus; UCTD, undifferentiated connective tissue disease.

as a result of the lack of definite classification criteria. For this reason, the therapeutic management of patients with UCTD mainly relies on the incorporation of treatment guidelines or common proxies for corresponding manifestations (such as arthritis or skin manifestations) that also occur in patients with defined rheumatic diseases such as SLE, RA, SSc and myositis. The main aim of early management is to reduce long-term complications related to delayed therapy, with the ultimate goal of minimizing irreversible organ damage and mortality. In an investigation of more than 9,000 patients with SLE, fewer flares and lower rates of hospitalization and overall SLE-related costs occurred in patients who were diagnosed within 6 months of the onset of clinical symptoms, compared with matched patients in whom diagnosis was delayed by more than 6 months[56]. These results suggest that the earlier the diagnosis, the greater the potential benefit with regard to disease-related damage.

Although some research efforts are currently ongoing that target patients with early-stage SLE[57,58], to date, no consensus exists on primary prevention in the management of individuals with preclinical SLE (patients with evidence of autoimmunity and immune dysregulation but with no clinical features of the disease). This lack of consensus is present because there is only limited evidence to support the idea that treatment in asymptomatic, ANA-positive individuals might prevent the development of a clinically relevant CTD. A retrospective study of US military personnel reported that the use of the antimalarial hydroxychloroquine prior to diagnosis

was associated with a delayed onset of SLE; of 130 individuals who met the 1997 ACR SLE classification criteria, those who had used hydroxychloroquine prior to diagnosis had a longer time between the onset of the first clinical symptom and SLE classification than those who had not used hydroxychloroquine (1.08 versus 0.29 years)[59]. Although these results seem promising, it should be kept in mind that, like any drug, antimalarial agents can have adverse events. Therefore, a careful evaluation of the balance between risk and benefit is warranted when considering the use of antimalarials as primary prevention in asymptomatic patients, as robust evidence to support their use in this setting are still lacking[56]. In patients with UCTD or early-stage SLE, although a potential role in the eventual development of definite SLE cannot be excluded, hydroxychloroquine use should be guided by clinical judgement and only used to try and control ongoing clinical manifestations, rather than as a primary prevention tool. Nevertheless, a growing body of evidence is currently emerging in which the role of different immunomodulatory or immunosuppressive approaches are investigated to mitigate SLE development in animal models[60,61]. The challenge for the future will be two-fold. On the one hand, strategies to avoid the progression to overt disease need to be developed for individuals at risk of SLE; on the other, reliable profiling approaches need to be developed for patients with SLE so that individuals at increased risk of developing specific organ involvement, such as lupus nephritis, can be identified and management approaches tuned accordingly.

From a practical point of view, close monitoring and appropriate counselling with the aim of removing potentially triggering factors (such as smoking, SLE-inducing drugs or excessive sunlight exposure) could be a reasonable approach for asymptomatic individuals who have persistent, isolated ANA positivity. The potential immunomodulatory role of vitamin D in reducing the risk of progression to a definite CTD is a subject of debate[62] but, at present, no solid evidence is available to support the systematic use of vitamin D supplementation in individuals who are potentially at risk of developing systemic autoimmune diseases. In asymptomatic ANA-positive individuals with SLE-associated autoantibodies (including anti-dsDNA, anti-Sm, anti-SSA/Ro or anti-SSB/La antibodies) and/or complement reduction (such as low concentrations of complement proteins C3 and/or C4), administering hydroxychloroquine could be considered a rational approach in an effort to reduce the risk of disease progression[63]. Positivity for other autoantibody specificities might also indicate potential for primary prevention, such as in asymptomatic carriers of antiphospholipid antibodies (aPLs),

Table 3 | **2012 SLICC classification criteria fulfilment in patients with early-stage SLE or UCTD**

Characteristic	Bortoluzzi et al. (2016)[15]	Aberle et al. (2017)[27]	Tiao et al. (2016)[95]	Overall range (%)
Demographics				
Number of patients	44	291	34	NA
Diagnosis	UCTD	Incomplete lupus erythematosus	Sub-acute CLE with SLE	NA
Clinical criteria (%)				
Acute cutaneous lupus	54.5	42.6	100.0	22.5–100.0
Chronic cutaneous lupus	0.0	8.9	NR	0.0–8.9
Oral or nasal ulcers	20.5	10.6	52.9	10.6–52.9
Non-scarring alopecia	29.5	0.7	11.8	0.7–29.5
Arthritis	31.8	45.0	58.8	31.8–58.8
Serositis	4.5	5.8	2.9	2.9–5.8
Renal disorder	0.0	4.5	13.8	0.0–13.8
Neurological disorder	15.9	1.4	8.8	1.4–15.9
Haemolytic anaemia	0.0	0.3	48.5	0.0–48.5
Leukopenia or lymphopenia	38.6	23.0	60.6	23.0–60.6
Thrombocytopenia	2.3	1.7	15.2	1.7–15.2
Immunological criteria (%)				
ANA	100.0	96.2	90.9	90.9–100.0
Anti-dsDNA antibodies	9.1	11.7	46.2	9.1–46.2
Anti-Sm antibodies	2.3	2.8	33.3	2.3–33.3
aPL	36.4	13.4	42.1	13.4–42.1
Low complement	75.0	1.0	55.6	1.0–75.0
Direct Coombs' test	0.0	0.0	NR	NA

Studies included in this table were mostly longitudinal studies with at least 20 patients. ANA, antinuclear antibody; aPL, antiphospholipid antibody; CLE, cutaneous lupus erythematosus; dsDNA, double-stranded DNA; NA, not applicable; NR, not reported; SLE, systemic lupus erythematosus; SLICC, systemic lupus international collaborating clinics; UCTD, undifferentiated connective tissue disease.

Table 4 | **Preferred nomenclature for SLE spectrum disorders and UCTD**

Term	Description	Example
At-risk of SLE	Genetic or environmental risk factors that pre-dispose the individual to SLE	25-year-old woman who has an identical twin with SLE but no features of the disease herself
Preclinical SLE	Evidence of autoimmunity and immune dysregulation but no clinical features of disease	25-year-old woman who is positive for ANA and anti-Sm antibodies but has no other features of SLE
Early SLE	Evidence of autoimmunity and some clinical features of SLE but fewer than required to meet classification criteria	25-year-old woman who is positive for ANA and anti-SSA/Ro antibodies and has a malar rash, but no other signs or symptoms of SLE
SLE	Symptoms, signs and laboratory features that meet classification criteria for SLE	25-year-old woman who is positive for ANA and anti-dsDNA antibodies and has lymphopenia, arthritis and lupus nephritis
UCTD	Evidence of autoimmunity and some clinical features of connective tissue diseases such as SLE, Sjögren syndrome, systemic sclerosis, rheumatoid arthritis or myositis, but not enough to meet the classification criteria for any of these conditions. Usually, disease has not progressed for at least 3 years with signs and symptoms remaining stable over time	25-year-old woman who is positive for ANA and has Raynaud phenomenon and sicca symptoms, but no other features of connective tissue diseases

ANA, antinuclear antibody; dsDNA, double-stranded DNA; SLE, systemic lupus erythematosus; UCTD, undifferentiated connective tissue disease.

particularly when high-risk thrombotic profiles are detected (such as multiple aPL specificities and/or high titres), because of the increased risk of thrombosis[64]. However, the intrinsic risk of bleeding associated with the chronic use of anti-thrombotic therapy should be evaluated. Similarly, in asymptomatic carriers of aPLs, time-limited anti-thrombotic prophylaxis (such as with low-molecular-weight heparin) could be evaluated in the context of potentially precipitating thrombotic factors (including surgery and long periods of immobilization) and would need to be carefully evaluated and managed by the treating clinician.

Future directions

Advancing diagnosis. To make progress towards improved diagnostic accuracy in the setting of UCTD, preclinical SLE and early-stage SLE, several factors need to be considered. First, the pathogenetic mechanisms that underlie the development of both the very early stages of a CTD and the progression from UCTD to a definite CTD need to be elucidated. Longitudinal studies of large, early-stage CTD and UCTD cohorts that include healthy volunteers and novel technologies such as multi-analyte platforms are needed to gain more understanding of how disease progresses. These emerging multi-analyte omics technologies have the potential to provide physicians with new biomarkers that could help them to understand the pathogenic processes that occur throughout the entire disease course[65]. Such technologies have the potential to shift the current reliance on trial and error towards a more accurate system of patient stratification, potentially guiding the design of new clinical trials and evidence-based individualized interventions[66].

Several technical issues also need to be addressed to improve diagnosis, such as the development of standardized follow-up testing algorithms for autoantibody profiling. The ANA indirect immunofluorescence test is currently the screening test of choice for UCTD, SLE and other CTDs, but in the future, follow-up testing algorithms could be used with multi-analyte solid phase assays to detect autoantibodies that recognize disease-specific targets in an efficient and economical way[67,68]. Although traditional thinking supports the concept that a positive test for even one autoantibody (such as ANA) suffices to suggest a diagnosis, a paradigm shift is needed to support the hypothesis that each autoantibody can provide added value for disease stratification and evidence-based approaches to therapy and prognosis, while, at the same time, providing value for accurate diagnosis. In terms of specificity, sensitivity and the predictive value of autoantibody testing, the accuracy of CTD diagnoses is predicted to increase by the application of artificial intelligence technologies to multi-analyte platforms, a paradigm shift referred to as multi-analytic arrays with algorithmic analyses[69].

The challenge for diagnostic approaches will be to identify those individuals who have the best chance of benefiting from a specific therapeutic agent[70,71]. Towards this aim, improvements in understanding of the molecular pathways that underlie autoimmune diseases are leading to the identification of biomarkers that could be used to identify patients with CTDs and ultimately guide novel therapeutic choices[72] (FIG. 2). Early modifications in the pro-inflammatory cytokine profile[73] precede the onset of clinical manifestations by a long time. For example, increases in IFNγ concentrations can precede a diagnosis of SLE by more than 3 years[74,75]. Interferons have a large number of effects on both the innate and the adaptive immune systems, and the importance of their role in autoimmunity is progressively being understood. Interferons can potentially influence the immune response at any level, from antigen-presenting cells to plasmacytoid dendritic cells to B cells and T cells. Moreover, IFNγ can trigger the production of interferogenic anti-RNA antibodies and can also cause an increase in type I interferons and a subsequent cascade of effects[74,75]. In a study of 57 individuals who tested positive for ANA who were compared with age-matched healthy individuals and patients with SLE, a stepwise increase occurred in the expression of pro-inflammatory cytokines (including IL-17, TNF and IFNγ) in which patients with SLE expressed the highest amounts and ANA-negative healthy individuals expressed the lowest, and only patients with SLE expressed high amounts of type I interferons[76]. This pattern of expression is connected with the role of type I interferons in SLE progression and self-maintenance[77]. However, an interferon signature can also be found in a substantial proportion of ANA-positive individuals who do not have a defined CTD[78]. This signature seems to be associated with the ANA titre and the type of autoantibody, instead of with the presence or development of clinical CTD symptoms[79]. All in all, although promising, the added

value of diagnostic testing for an interferon signature will require further studies to be fully elucidated.

Advancing nomenclature. Despite advances in our understanding of the immune dysregulation that underlies SLE, diagnosing and classifying the condition remain challenging. The use of nomenclature to define individuals with only some features of the disease or with features that overlap with other autoimmune conditions has been inconsistent, with terms such as occult, incomplete, incipient, possible, latent and probable SLE being used, in addition to UCTD. Future definitions of SLE-spectrum disorders should have a higher specificity than current definitions as increasingly more molecular data become available with which to define disease subgroups. In the meantime, working towards a common nomenclature will be important, both for organizing clinical reasoning and for correctly identifying subsets of patients (TABLE 4).

As we move towards an improved definition of UCTD, several observational studies are currently ongoing with the aim of gathering information about clinical symptoms and laboratory test results in patients with this condition[79–81]. Analysis of the results of such studies could help researchers to better predict the prognosis for patients with this form of autoimmune disease, and could also help to identify risk factors for progression to more specific CTDs, such as SLE. In the meantime, from a clinical point of view, the time from the onset of the symptoms and/or serological abnormalities to diagnosis might represent a good indicator to help in retrospectively differentiating early-stage SLE from stable UCTD. Similarly, from a practical perspective for research studies, one could consider using the term 'early SLE', which is more specific than the term incomplete SLE, to identify those patients with features that are strongly suggestive of SLE who do not have classifiable SLE (for example, a young woman with positive tests for ANA and anti-dsDNA antibodies and a malar rash, but no other signs or symptoms of SLE).

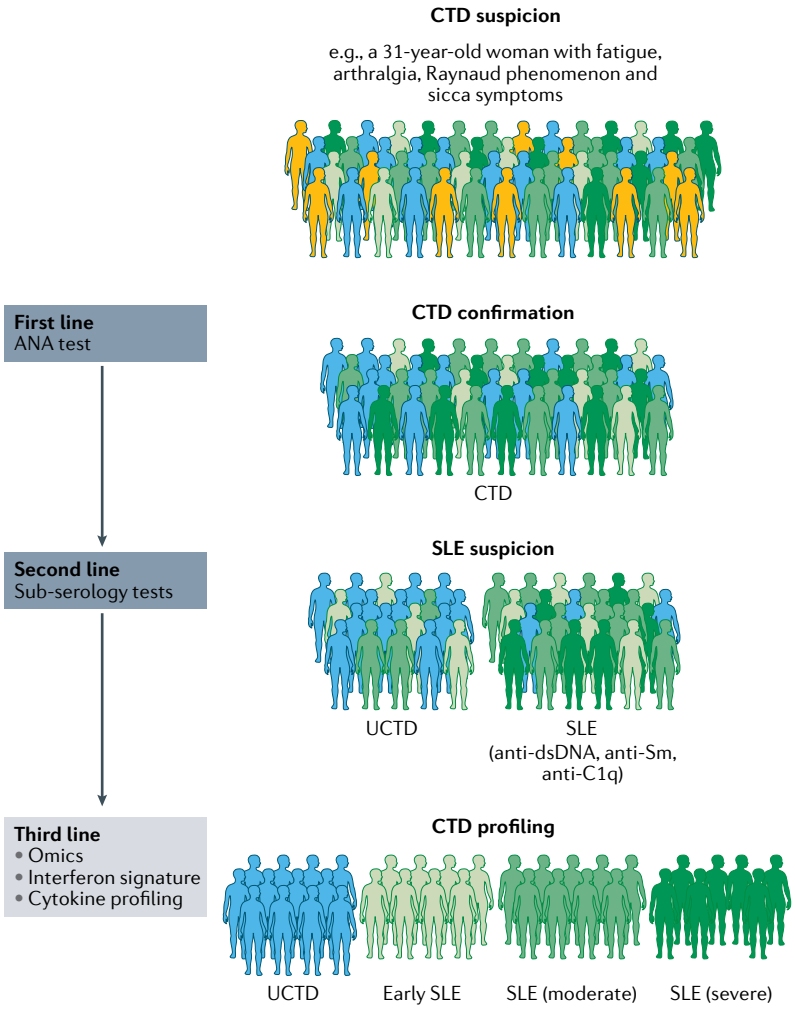

Fig. 2 | **From screening and diagnosis to patient phenotyping.** Different levels of laboratory diagnostic pathways can help physicians to correctly identify patients with undifferentiated connective tissue disease (UCTD) and patients with systemic lupus erythematosus (SLE). First-line tests should help physicians to identify those with a connective tissue disease (CTD) from among all patients with a suspected rheumatic condition. In this phase, the presence of a positive antinuclear antibody (ANA) test result and associated hypocomplementaemia can support the diagnosis of a CTD. Second-line testing is aimed at identifying those individuals who are most likely to have SLE or to develop it in the near future. In the future, third-line testing, which could potentially include omics approaches, testing for an interferon signature and cytokine profiling, has the potential to further improve the accuracy of diagnosis, prognosis (for example, differentiating mild from severe SLE) and, more critically, to guide tailored therapeutic approaches. Starting from the current state of the art, this figure presents a model that could potentially be implemented using tests that are likely to be widely available in the near future. C1q, complement protein C1q; dsDNA, double-stranded DNA.

Conclusions

In clinical practice, it is not uncommon to find individuals with clinical and serological features that are suggestive of an autoimmune condition, but that are not sufficient for a diagnosis with a defined CTD. The nomenclature that has been used to define such individuals over the years has been inconsistent, limiting the comparability of available studies. Although the clinical manifestations of UCTD, early-stage SLE and definite SLE might overlap at certain times during the disease course, differentiating among these conditions is crucial in order to provide tailored follow-up and management for these patients. The challenge for the future will be to develop a shared consensus beyond available classification criteria to identify clinical variables and disease-specific antibody profiles (taking into account how these might change over time) to predict the progression of UCTD and early SLE to a definite CTD. An update of the available classification criteria for UCTD is highly desirable, as is the development of response criteria for evaluating meaningful changes in disease status in patients with UCTD that can be used in clinical trials and possibly also in clinical practice. For SLE-spectrum disorders, more specific definitions need to be developed that make use of molecular data to define disease subgroups. Ultimately, the goal for the future should be to help the treating physician to stratify patients who are clinically similar at first presentation into subgroups according to their baseline signs, symptoms and serological profile in order to design tailored diagnostic and therapeutic pathways.

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1. Wandstrat, A. E. et al. Autoantibody profiling to identify individuals at risk for systemic lupus erythematosus. *J. Autoimmun.* **27**, 153–160 (2006).
2. Antunes, M. et al. Undifferentiated connective tissue disease: state of the art on clinical practice guidelines. *RMD Open.* **4** (Suppl. 1), e000786 (2019).
3. Combe, B. et al. 2016 update of the EULAR recommendations for the management of early arthritis. *Ann. Rheum. Dis.* **76**, 948–959 (2017).
4. Kamataki, N. et al. Complement genes contribute sex-biased vulnerability in diverse disorders. *Nature* **582**, 577–581 (2020).
5. Zhao, Z. et al. Nature of T cell epitopes in lupus antigens and HLA-DR determines autoantibody initiation and diversification. *Ann. Rheum. Dis.* **78**, 380–390 (2019).
6. Jog, N. R. et al. Association of Epstein-Barr virus serological reactivation with transitioning to systemic lupus erythematosus in at-risk individuals. *Ann. Rheum. Dis.* **78**, 1235–1241 (2019).
7. Mosca, M., Tani, C. & Bombardieri, S. Undifferentiated connective tissue diseases (UCTD): a new frontier for rheumatology. *Best. Pract. Res. Clin. Rheumatol.* **21**, 1011–1023 (2007).
8. Carneiro, A. C., Ruiz, M. M., Freitas, S. & Isenberg, D. A comparison of three classification criteria sets for systemic lupus erythematosus–a study looking at links to outcome and mortality. *Arthritis Care Res.* **72**, 1611–1614 (2019).
9. Adamichou, C. et al. In an early SLE cohort the ACR-1997, SLICC-2012 and EULAR/ACR-2019 criteria classify non-overlapping groups of patients: use of all three criteria ensures optimal capture for clinical studies while their modification earlier classification and treatment. *Ann. Rheum. Dis.* **79**, 232–241 (2020).
10. Aringer, M. et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann. Rheum. Dis.* **78**, 1151–1159 (2019).
11. Mosca, M., Neri, R. & Bombardieri, S. Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. *Clin. Exp. Rheumatol.* **17**, 615–620 (1999).
12. Mosca, M., Tani, C., Carli, L. & Bombardieri, S. Undifferentiated CTD: a wide spectrum of autoimmune diseases. *Best. Pract. Res. Clin. Rheumatol.* **26**, 73–77 (2012).
13. Mosca, M., Tani, C., Talarico, R. & Bombardieri, S. Undifferentiated connective tissue diseases (UCTD): simplified systemic autoimmune diseases. *Autoimmun. Rev.* **10**, 256–258 (2011).
14. Radin, M. et al. A multicentre study of 244 pregnancies in undifferentiated connective tissue disease: maternal/foetal outcomes and disease evolution. *Rheumatology* **59**, 2412–2418 (2020).
15. Bortoluzzi, A., Furini, F., Campanaro, F. & Govoni, M. Application of SLICC classification criteria in undifferentiated connective tissue disease and evolution in systemic lupus erythematosus: analysis of a large monocentric cohort with a long-term follow-up. *Lupus* **26**, 616–622 (2017).
16. Vaz, C. C. et al. Undifferentiated connective tissue disease: a seven-center cross-sectional study of 184 patients. *Clin. Rheumatol.* **28**, 915–921 (2009).
17. Mosca, M., Tani, C., Vagnani, S., Carli, L. & Bombardieri, S. The diagnosis and classification of undifferentiated connective tissue diseases. *J. Autoimmun.* **48–49**, 50–52 (2014).
18. Bourn, R. & James, J. A. Preclinical lupus. *Curr. Opin. Rheumatol.* **27**, 433–439 (2015).
19. Radin, M. et al. Impact of the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology classification criteria for systemic lupus erythematosus in a multicenter cohort study of 133 women with undifferentiated connective tissue disease. *Arthritis Care Res.* https://doi.org/10.1002/acr.24391 (2020).
20. Hallengren, C. S., Nived, O. & Sturfelt, G. Outcome of incomplete systemic lupus erythematosus after 10 years. *Lupus* **13**, 85–88 (2004).
21. Md Yusof, M. Y. et al. Prediction of autoimmune connective tissue disease in an at-risk cohort: prognostic value of a novel two-score system for interferon status. *Ann. Rheum. Dis.* **77**, 1432–1439 (2018).
22. Mosca, M., Tavoni, A., Neri, R., Bencivelli, W. & Bombardieri, S. Undifferentiated connective tissue diseases: the clinical and serological profiles of 91 patients followed for at least 1 year. *Lupus* **7**, 95–100 (1998).
23. Rúa-Figueroa, Í. et al. Comprehensive description of clinical characteristics of a large systemic lupus erythematosus cohort from the Spanish Rheumatology Society Lupus Registry (RELESSER) with emphasis on complete versus incomplete lupus differences. *Medicine* **94**, e267 (2015).
24. Rasmussen, A. et al. The lupus family registry and repository. *Rheumatology* **50**, 47–59 (2011).
25. Tan, E. M. et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* **25**, 1271–1277 (1982).
26. Petri, M. et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum.* **64**, 2677–2686 (2012).
27. Aberle, T. et al. Use of SLICC criteria in a large, diverse lupus registry enables SLE classification of a subset of ACR-designated subjects with incomplete lupus. *Lupus Sci. Med.* **4**, e000176 (2017).
28. Chen, Z. et al. Organ damage in patients with incomplete lupus syndromes: from a Chinese academic center. *Clin. Rheumatol.* **34**, 1383–1389 (2015).
29. Rees, F. et al. Early clinical features in systemic lupus erythematosus: can they be used to achieve earlier diagnosis? A risk prediction model. *Arthritis Care Res.* **69**, 833–841 (2017).
30. García-González, M., Rodríguez-Lozano, B., Bustabad, S. & Ferraz-Amaro, I. Undifferentiated connective tissue disease: predictors of evolution into definite disease. *Clin. Exp. Rheumatol.* **35**, 739–745 (2017).
31. Drehmel, K. R. et al. Applying SLICC and ACR/EULAR systemic lupus erythematosus classification criteria in a cohort of patients with undifferentiated connective tissue disease. *Lupus* **30**, 280–284 (2021).
32. Mosca, M. et al. Brief report: how do patients with newly diagnosed systemic lupus erythematosus present? A multicenter cohort of early systemic lupus erythematosus to inform the development of new classification criteria. *Arthritis Rheumatol.* **71**, 91–98 (2019).
33. Nightingale, A. L., Davidson, J. E., Molta, C. T., Kan, H. J. & McHugh, N. J. Presentation of SLE in UK primary care using the Clinical Practice Research Datalink. *Lupus Sci. Med.* **4**, e000172 (2017).
34. Negrini, S. et al. Sjögren's syndrome: a systemic autoimmune disease. *Clin. Exp. Med.* https://doi.org/10.1007/S10238-021-00728-6 (2021).
35. Sebastiani, M. et al. Interstitial pneumonia with autoimmune features: why rheumatologist-pulmonologist collaboration is essential. *Biomedicines* **9**, 17 (2020).
36. Fischer, A. Interstitial pneumonia with autoimmune features. *Clin. Chest Med.* **40**, 609–616 (2019).
37. Satoh, M. et al. Clinical implication of autoantibodies in patients with systemic rheumatic diseases. *Expert Rev. Clin. Immunol.* **3**, 721–738 (2007).
38. Arbuckle, M. R. et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N. Engl. J. Med.* **349**, 1526–1533 (2003).
39. Lu, R. et al. Dysregulation of innate and adaptive serum mediators precedes systemic lupus erythematosus classification and improves prognostic accuracy of autoantibodies. *J. Autoimmun.* **74**, 182–193 (2016).
40. Landolt-Marticorena, C. The need for preclinical biomarkers in systemic autoimmune rheumatic diseases. *J. Rheumatol.* **42**, 152–154 (2015).
41. Cavazzana, I. et al. Undifferentiated connective tissue disease with antibodies to Ro/SSa: clinical features and follow-up of 148 patients. *Clin. Exp. Rheumatol.* **19**, 403–409 (2001).
42. Belfiore, N. et al. Anti-Ro(SS-A) 52 kDa and 60 kDa specificities in undifferentiated connective tissue disease. *Jt. Bone Spine* **67**, 183–187 (2000).
43. Murng, S. H. K. & Thomas, M. Clinical associations of the positive anti Ro52 without Ro60 autoantibodies: undifferentiated connective tissue diseases. *J. Clin. Pathol.* **71**, 12–19 (2018).
44. Alarcõn, G. S. et al. Early undifferentiated connective tissue disease. I. Early clinical manifestation in a large cohort of patients with undifferentiated connective tissue diseases compared with cohorts of well established connective tissue disease. *J. Rheumatol.* **18**, 1332–1339 (1991).
45. McClain, M. T. et al. The prevalence, onset, and clinical significance of antiphospholipid antibodies prior to diagnosis of systemic lupus erythematosus. *Arthritis Rheum.* **50**, 1226–1232 (2004).
46. Van Gaalen, F. A. et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum.* **50**, 709–715 (2004).
47. Allenbach, Y., Benveniste, O., Goebel, H. H. & Stenzel, W. Integrated classification of inflammatory myopathies. *Neuropathol. Appl. Neurobiol.* **43**, 62–81 (2017).
48. Andrejevic, S. et al. Immunoserological parameters in SLE: high-avidity anti-dsDNA detected by ELISA are the most closely associated with the disease activity. *Clin. Rheumatol.* **32**, 1619–1626 (2013).
49. Aletaha, D. et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann. Rheum. Dis.* **69**, 1580–1588 (2010).
50. Biliavska, I. et al. Application of the 2010 ACR/EULAR classification criteria in patients with very early inflammatory arthritis: analysis of sensitivity, specificity and predictive values in the SAVE study cohort. *Ann. Rheum. Dis.* **72**, 1335–1341 (2013).
51. Avouac, J. et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi consensus study from EULAR scleroderma trials and research group. *Ann. Rheum. Dis.* **70**, 476–481 (2011).
52. Low, E. S. H., Krishnaswamy, G. & Thumboo, J. Comparing the 1997 update of the 1982 American College of Rheumatology (ACR-97) and the 2012 Systemic Lupus International Collaborating Clinics (SLICC-12) criteria for systemic lupus erythematosus (SLE) classification: which enables earlier classification. *Lupus* **28**, 11–18 (2019).
53. Gatto, M., Saccon, F., Zen, M., Iaccarino, L. & Doria, A. Preclinical and early systemic lupus erythematosus. *Best. Pract. Res. Clin. Rheumatol.* **33**, 101422 (2019).
54. Robertson, J. M. & James, J. A. Preclinical systemic lupus erythematosus. *Rheum. Dis. Clin. North. Am.* **40**, 621–635 (2014).
55. Trapiella-Martínez, L. et al. Very early and early systemic sclerosis in the Spanish scleroderma Registry (RESCLE) cohort. *Autoimmu. Rev.* **16**, 796–802 (2017).
56. Oglesby, A. et al. Impact of early versus late systemic lupus erythematosus diagnosis on clinical and economic outcomes. *Appl. Health Econ. Health Policy* **12**, 179–190 (2014).
57. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03543839 (2020).
58. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03804723 (2019).
59. James, J. A. et al. Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus. *Lupus* **16**, 401–409 (2007).
60. Yan, Q. et al. Prevention of immune nephritis by the small molecular weight immunomodulator iguratimod in MRL/lpr mice. *PLoS ONE* **9**, e108273 (2014).
61. Perper, S. J. et al. Treatment with a CD40 antagonist antibody reverses severe proteinuria and loss of saliva production and restores glomerular morphology in murine systemic lupus erythematosus. *J. Immunol.* **203**, 58–75 (2019).
62. Durcan, L. & Petri, M. Immunomodulators in SLE: clinical evidence and immunologic actions. *J. Autoimmun.* **74**, 73–84 (2016).
63. Doria, A. et al. SLE diagnosis and treatment: when early is early. *Autoimmun. Rev.* **10**, 55–60 (2010).
64. Pengo, V. et al. What have we learned about antiphospholipid syndrome from patients and antiphospholipid carrier cohorts? *Semin. Thromb. Hemost.* **38**, 322–327 (2012).
65. El-Sherbiny, Y. M. et al. A novel two-score system for interferon status segregates autoimmune diseases and correlates with clinical features. *Sci. Rep.* **8**, 5793 (2018).
66. Pisetsky, D. S., Rovin, B. H. & Lipsky, P. E. New perspectives in rheumatology: biomarkers as entry criteria for clinical trials of new therapies for systemic lupus erythematosus: the example of antinuclear antibodies and anti-DNA. *Arthritis Rheumatol.* **69**, 487–493 (2017).
67. Pérez, D. et al. Antinuclear antibodies: is the indirect immunofluorescence still the gold standard or should be replaced by solid phase assays? *Autoimmun. Rev.* **17**, 548–552 (2018).
68. van Vollenhoven, R. F. et al. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. *Lancet* **392**, 1330–1339 (2018).

69. Banchereau, R. et al. Personalized immunomonitoring uncovers molecular networks that stratify lupus patients. *Cell* **165**, 551–565 (2016).
70. Agarwal, A., Ressler, D. & Snyder, G. The current and future state of companion diagnostics. *Pharmacogenomics Pers. Med.* **8**, 99–110 (2015).
71. Jørgensen, J. T. & Hersom, M. Companion diagnostics — a tool to improve pharmacotherapy. *Ann. Transl. Med.* **4**, 482 (2016).
72. Kraus, V. B. Biomarkers as drug development tools: discovery, validation, qualification and use. *Nat. Rev. Rheumatol.* **14**, 354–362 (2018).
73. Munroe, M. E. et al. Altered type II interferon precedes autoantibody accrual and elevated type I interferon activity prior to systemic lupus erythematosus classification. *Ann. Rheum. Dis.* **75**, 2014–2021 (2016).
74. Chyuan, I.-T., Tzeng, H.-T. & Chen, J.-Y. Signaling pathways of type I and type III interferons and targeted therapies in systemic lupus erythematosus. *Cells* **8**, 963 (2019).
75. Gallucci, S., Meka, S. & Gamero, A. M. Abnormalities of the type I interferon signaling pathway in lupus autoimmunity. *Cytokine* **146**, 155633 (2021).
76. Slight-Webb, S. et al. Autoantibody-positive healthy individuals display unique immune profiles that may regulate autoimmunity. *Arthritis Rheumatol.* **68**, 2492–2502 (2016).
77. Luo, S., Wang, Y., Zhao, M. & Lu, Q. The important roles of type I interferon and interferon-inducible genes in systemic lupus erythematosus. *Int. Immunopharmacol.* **40**, 542–549 (2016).
78. Wither, J. et al. Presence of an interferon signature in individuals who are anti-nuclear antibody positive lacking a systemic autoimmune rheumatic disease diagnosis. *Arthritis Res. Ther.* **19**, 41 (2017).
79. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02234388 (2021).
80. US National Library of Medicine. *Clinicaltrials.gov* https://clinicaltrials.gov/ct2/show/NCT03671174 (2019).
81. US National Library of Medicine. *Clinicaltrials.gov* https://clinicaltrials.gov/ct2/show/NCT04402086 (2021).
82. Greer, J. M. Incomplete lupus erythematosus. *Arch. Intern. Med.* **149**, 2473 (1989).
83. Swaak, A. J. et al. Incomplete lupus erythematosus: results of a multicentre study under the supervision of the EULAR Standing Committee on International Clinical Studies Including Therapeutic Trials (ESCISIT). *Rheumatology* **40**, 89–94 (2001).
84. Laustrup, H., Voss, A., Green, A. & Junker, P. SLE disease patterns in a Danish population-based lupus cohort: an 8-year prospective study. *Lupus* **19**, 239–246 (2010).
85. Olsen, N. J. et al. Autoantibody profiling to follow evolution of lupus syndromes. *Arthritis Res. Ther.* **14**, R174 (2012).
86. Calvo-Alen, J. et al. Systemic lupus erythematosus: predictors of its occurrence among a cohort of patients with early undifferentiated connective tissue disease: multivariate analyses and identification of risk factors. *J. Rheumatol.* **23**, 469–475 (1996).
87. Danieli, M. G., Fraticelli, P., Salvi, A., Gabrielli, A. & Danieli, G. Undifferentiated connective tissue disease: natural history and evolution into definite CTD assessed in 84 patients initially diagnosed as early UCTD. *Clin. Rheumatol.* **17**, 195–201 (1998).
88. Danieli, M. G. et al. Five-year follow-up of 165 Italian patients with undifferentiated connective tissue diseases. *Clin. Exp. Rheumatol.* **17**, 585–591 (1999).
89. Williams, H. J. et al. Early undifferentiated connective tissue disease (CTD). VI. An inception cohort after 10 years: disease remissions and changes in diagnoses in well established and undifferentiated CTD. *J. Rheumatol.* **26**, 816–825 (1999).
90. Bodolay, E. et al. Five-year follow-up of 665 Hungarian patients with undifferentiated connective tissue disease (UCTD). *Clin. Exp. Rheumatol.* **21**, 313–230 (2003).
91. Guerrero, L. F., Rueda, J. C., Arciniegas, R. & Rueda, J. M. Undifferentiated connective tissue disease in a rheumatology center in Cali, Colombia: clinical features of 94 patients followed for a year. *Rheumatol. Int.* **33**, 1085–1088 (2013).
92. Zucchi, D. et al. Pregnancy and undifferentiated connective tissue disease: outcome and risk of flare in 100 pregnancies. *Rheumatology* **59**, 1335–1339 (2020).
93. Ganczarczyk, L., Urowitz, M. B. & Gladman, D. D. "Latent lupus". *J. Rheumatol.* **4**, 475–478 (1989).
94. Al Daabil, M. et al. Development of SLE among 'potential SLE' patients seen in consultation: long-term follow-up. *Int. J. Clin. Pract.* **68**, 1508–1513 (2014).
95. Tiao, J., Feng, R., Carr, K., Okawa, J. & Werth, V. P. Using the American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC) criteria to determine the diagnosis of systemic lupus erythematosus (SLE) in patients with subacute cutaneous lupus erythematosus (SCLE). *J. Am. Acad. Dermatol.* **74**, 862–869 (2016).
96. Ramsey-Goldman, R. et al. Complement activation in patients with probable systemic lupus erythematosus and ability to predict progression to American College of Rheumatology-classified systemic lupus erythematosus. *Arthritis Rheumatol.* **72**, 78–88 (2020).
97. Spinillo, A. et al. Prevalence of undiagnosed autoimmune rheumatic diseases in the first trimester of pregnancy. Results of a two-steps strategy using a self-administered questionnaire and autoantibody testing. *BJOG* **115**, 51–57 (2008).
98. Mosca, M. et al. Pregnancy outcome in patients with undifferentiated connective tissue disease: a preliminary study on 25 pregnancies. *Lupus* **11**, 304–307 (2002).
99. Spinillo, A. et al. The effect of newly diagnosed undifferentiated connective tissue disease on pregnancy outcome. *Am. J. Obstet. Gynecol.* **199**, 632.e1–632.e6 (2008).
100. Grava, C. et al. Isolated congenital heart block in undifferentiated connective tissue disease and in primary Sjögren's syndrome: a clinical study of 81 pregnancies in 41 patients [Italian]. *Reumatismo* **57**, 180–186 (2005).
101. Castellino, G. et al. Pregnancy in patients with undifferentiated connective tissue disease: a prospective case-control study. *Lupus* **20**, 1305–1311 (2011).
102. Spinillo, A. et al. The impact of unrecognized autoimmune rheumatic diseases on the incidence of preeclampsia and fetal growth restriction: a longitudinal cohort study. *BMC Pregnancy Childbirth* **16**, 313 (2016).
103. Fredi, M. et al. First report of the Italian registry on immune-mediated congenital heart block (Lu.Ne Registry). *Front. Cardiovasc. Med.* **6**, 11 (2019).
104. Brito-Zerón, P., Izmirly, P. M., Ramos-Casals, M., Buyon, J. P. & Khamashta, M. A. The clinical spectrum of autoimmune congenital heart block. *Nat. Rev. Rheumatol.* **11**, 301–312 (2015).
105. Schreiber, K., Radin, M. & Sciascia, S. Current insights in obstetric antiphospholipid syndrome. *Curr. Opin. Obstet. Gynecol.* **29**, 397–403 (2017).
106. Andreoli, L. et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann. Rheum. Dis.* **76**, 476–485 (2017).

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Review criteria
PubMed was searched for English-language, full-text articles published between January 1979 and June 2020 using the following terms: "systemic lupus erythematosus", "undifferentiated connective tissue disease", "early lupus", "pre-lupus" and "lupus". Longitudinal studies that included at least 20 patients were given preference. Additional articles were found by searching the reference lists of identified articles, and some abstracts and meeting reports were also analysed.

Global epidemiology of vasculitis

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Abstract | The many forms of vasculitis are characterized by inflammation of blood vessels, leading to potentially long-term sequelae including vision loss, aneurysm formation and kidney failure. Accurate estimation of the incidence and prevalence has been hampered by the absence of reliable diagnostic criteria and the rarity of these conditions; however, much progress has been made over the past two decades, although data are still lacking from many parts of the world including the Indian subcontinent, China, Africa and South America. Giant cell arteritis occurs in those aged 50 years and over and seems to mainly affect persons of northern European ancestry, whereas Takayasu arteritis occurs mainly in those aged under 40 years. By contrast, Kawasaki disease mainly occurs in children aged under 5 years and is most common in children of Asian ancestry, and IgA vasculitis occurs in children and adolescents. Although much less common than giant cell arteritis, the different forms of antineutrophil cytoplasmic antibody-associated vasculitis are being increasingly recognized in most populations and occur more frequently with increasing age. Behçet syndrome occurs most commonly along the ancient silk road between Europe and China. Much work needs to be done to better understand the influence of ethnicity, geographical location, environment and social factors on the development of vasculitis.

Systemic vasculitis is a term that covers a group of rare conditions characterized by inflammation of blood vessels, which leads to organ ischaemia and damage. Vasculitis can affect individuals of all ages, but certain conditions show a marked age tropism; for example, Kawasaki disease affects young children, whereas giant cell arteritis (GCA) predominantly affects those aged >50 years. The reasons for these differences are in general unknown but might reflect interactions between a widespread environmental trigger and a genetically predisposed child in Kawasaki disease and interactions between infection and 'immunosenescence' in the ageing immune system in GCA[1,2]. Although much is now known about the immunopathogenesis of vasculitis, relatively little is known about the events leading up to the development of clinical disease. Classic descriptive epidemiology can provide some clues, for example, by demonstrating evidence of clustering or a cyclical pattern of occurrence that might indicate a possible infectious aetiology. However, the rarity of the conditions has posed a number of methodological problems, together with uncertainty as to case definition.

Reliable classification criteria are an absolute requirement for conducting accurate epidemiology, yet there has been no universal system of classification for vasculitis. Vasculitis is defined according to the predominant size of the vessel involved[3]. Large vessels include the aorta and its major branches, medium vessels include the main visceral arteries and their branches, and small vessels include intraparenchymal arteries, arterioles, capillaries and venules. The ACR promulgated classification criteria for seven types of vasculitis in 1990, but these criteria were subsequently shown to be unreliable following developments in imaging and autoantibody serology[4,5]. The criteria were developed using patients from North America without representation from Europe or Asia, which is clearly not appropriate for conditions that have geographical variation in the pattern of disease. The Chapel Hill Consensus conferences of 1994 and 2012 produced definitions that are widely used in clinical studies, but these were not designed for use as classification criteria[3,6]. New classification criteria for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and large vessel vasculitis have been developed over the past decade[7]. Those for AAV will be published during 2022. It is hoped that these will provide a secure basis from which to conduct future studies[8–10].

Two main types of study have been used to assess the incidence and prevalence of vasculitis: cohort studies and registry studies. Cohort studies have the benefit that case classification can be confirmed, the downside being that it can take a long time to accumulate enough cases to conduct an accurate study. The geographical location from which the study population is drawn also needs to be tightly defined to ensure complete case capture. By contrast, registry studies have the advantage that a large number of cases can be identified rapidly from large populations, but confirmation of case classification is often impossible. Statistical methods such

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Key points

- Vasculitis is a group of generally uncommon diseases of generally unknown aetiology.
- Vasculitis mainly occurs at the ends of the age spectrum, in young children and older adults.
- Kawasaki disease is most common in children aged 5 years or less and occurs most commonly in Japan and in children of Southeast Asian ancestry.
- Giant cell arteritis is the most common form of vasculitis in elderly individuals, particularly in those of Northern European ancestry.
- The three types of antineutrophil cytoplasmic antibody-associated vasculitis are rare; of the three types, granulomatosis with polyangiitis is the most prevalent.
- Behçet syndrome has the highest prevalence along the ancient silk road, which stretches from the Mediterranean through the Middle East to East Asia.

as capture–recapture analysis enable the identification of cases that might have been missed, but are only possible where potential cases can be identified from multiple independent sources[11]. Differences in study design are therefore considered to be responsible for some of the variation in prevalence seen between geographical regions. For example, a study in which the effect of methodology on the geographic variation in Behçet syndrome prevalence was explored concluded that studies that used a sample survey design reported strikingly greater prevalence rates than studies with a census design[12]. Furthermore, the structure of many health-care systems does not lend itself to epidemiological studies. Regions with well-developed comprehensive state insurance-based systems are good locations for registry studies, whereas those with more fragmented systems can often only produce centre-based studies or registries based on private insurance systems. Reliable data are therefore lacking from many regions, particularly Africa, the Indian subcontinent, China and Latin America. Importantly, this lack of data does not mean that the conditions do not occur in these locations, just that the tools for measuring disease occurrence and burden are not available.

In this Review, we examine the occurrence of types of vasculitis that are of particular relevance to rheumatologists (TABLE 1), focusing on large vessel vasculitis (Takayasu arteritis and GCA), medium vessel vasculitis (polyarteritis nodosa and Kawasaki disease), small vessel vasculitis (AAV, IgA vasculitis and hypocomplementaemic urticarial vasculitis) and Behçet syndrome, across the globe to develop an overview of the current burden of disease.

Large vessel vasculitis

Large vessel vasculitis encompasses Takayasu arteritis and GCA, which are conditions that cause inflammation of the aorta and its major branches[3]. There has been considerable debate as to whether these two conditions are distinct or represent a spectrum[13]. The 1990 ACR classification criteria included strict age criteria of ≤40 years for Takayasu arteritis and ≥50 years for GCA[14,15]. However, many patients with Takayasu arteritis present after a considerable delay after the age of 40 years, making application of the criteria challenging. The patterns of arterial involvement also overlap, making distinction on clinical grounds difficult[16].

Takayasu arteritis. Compared with GCA, there are relatively few data on the occurrence of Takayasu arteritis. In addition, there is often a long diagnostic delay, which makes incidence studies unreliable. The annual incidence rate is in the range 0.4–3.4 per million people with a female predominance, although the majority of studies have been in white populations from Northern Europe[17–21]. Takayasu arteritis was originally described in Japan and it has long been considered that the occurrence is greatest in individuals from Southeast Asia. Data from the 1980s from Japan suggest that the incidence rate there is similar to that seen in Europe (1–2 per million people per year)[22]. A 2021 systematic meta-analysis estimated the incidence rate to be 1.11 per million person years (95% CI 0.70–1.76), although considerable heterogeneity in data was noted, suggesting substantial variation in incidence rates across different populations[23].

Studies from the past 10 years suggest prevalence figures of 8.4 per million in the USA[24], 9.0 per million in Italy[25], 13.2 per million in Sweden[19], 14.5 per million in Switzerland[26] and 25.2 per million in Norway[18], which are approaching those seen in Japan (40.0 per million), South Korea (28.2 per million) and Turkey (33.0 per million)[21,27,28]. Studies from Scandinavia report a higher prevalence in people of non-Northern European ancestry than in those with Scandinavian ancestry[18,19]. In Norway, there was a 3.5-fold to 5.0-fold difference in prevalence between individuals of Northern European ancestry (22.0 per million) and those of Asian ancestry (78.1 per million) or African ancestry (108.3 per million)[18]. However, interpretation of these studies is limited by the small numbers of patients in the non-Scandinavian populations included.

Giant cell arteritis. GCA is a common systemic vasculitis in adults aged >50 years[29]. Cranial GCA is characterized by acute onset headache, scalp tenderness, jaw claudication and visual loss. Patients with extracranial GCA have a more severe systemic illness with fever, weight loss, aortitis and involvement of peripheral arteries. Permanent blindness is the most feared long-term sequela of untreated GCA, occurring in up to 30% of patients[30]. Modern imaging techniques, including positron emission tomography, computed tomography and vascular ultrasonography, have demonstrated that extra-cranial large vessel involvement is much more common than was previously recognized, occurring in up to 83% of patients[31]. Furthermore, a subset of patients with GCA present with systemic illness without classic features of cranial GCA[32]. The epidemiological characteristics of this phenotype are not well described and might overlap with cranial GCA and with Takayasu arteritis. In some regions, vascular imaging (particularly ultrasonography of temporal arteries) is replacing traditional temporal artery biopsy (TAB) for GCA diagnosis, but vascular imaging is not routinely undertaken in all regions and centres. The 1990 ACR criteria for GCA do not include vascular imaging[15], although the performance of the criteria can be improved by including imaging[33]. New joint ACR–EULAR criteria are currently being developed that will address this issue[7].

GCA is well known as a disease that is more common in populations with Northern European ancestry (FIG. 1a, Supplementary Table 1). Comparable epidemiological features have been reported in Scandinavian and Northern American populations, particularly in areas of North America with immigrants from Scandinavia[34,35]. However, globally, the majority of studies have reported on populations with Northern European ancestry, and it is possible that the apparently higher frequency of GCA in Northern Europe is an artefact of the populations studied. A 2021 meta-analysis of studies that included more than 50 cases and that were published before 2019 reported an overall pooled incidence of GCA of 10.0 per 100,000 in people aged ≥50 years, with the highest incidence in Scandinavia (21.6 per 100,000) followed by North and South America (10.89 per 100,000), Oceania (7.8 per 100,000) and Europe (7.3 per 100,000)[29]. This meta-analysis confirmed the previously reported association of latitude with incidence but not with prevalence or mortality[36]. Notably, the association of incidence with latitude is independent of the increased frequency of *HLA-DRB1*04* (a GCA susceptibility allele) in Northern European populations[36].

The reported epidemiological characteristics of GCA vary worldwide depending on the case definition used, as some studies only include patients with TAB-confirmed GCA, whereas others rely on clinical manifestations and include patients who fulfil the 1990 ACR classification criteria, which do not mandate confirmatory histology[15], or patients with evidence of large vessel vasculitis from imaging studies. As expected, studies that use clinical and histological data yield slightly higher incidence figures than those that do not; in a systematic review, the mean incidence rate of GCA in European studies using only patients with a positive TAB was 14.6 per 100,000 persons aged ≥50 years (range 6.0–43.6) compared with 15.2 per 100,000 in studies that used broader clinical criteria[37]. However, the incidence

Table 1 | **Characteristics of different types of vasculitis**

Type of vasculitis	Age tropism	Affected vessels	Pathology	Major clinical features
Large vessel vasculitis				
Takayasu arteritis	<50 years	Aorta and its major branches	Granulomatous arteritis	Limb claudication, pulse loss and systemic illness
Giant cell arteritis	>60 years	Predilection for the branches of the carotid and vertebral arteries, especially the temporal arteries	Granulomatous arteritis with giant cells	Headache, polymyalgia rheumatica, constitutional symptoms, visual disturbance and limb claudication
Medium vessel vasculitis				
Polyarteritis nodosa	None	Medium or small arteries	Necrotizing arteritis	Mononeuritis multiplex, testicular pain and skin ulceration; associated with HBV infection; not associated with glomerulonephritis or ANCAs
Kawasaki disease	<5 years	Medium and small arteries, especially coronary arteries	Pan arteritis	Mucocutaneous lymph node syndrome and coronary artery aneurysms
Small vessel vasculitis				
Granulomatosis with polyangiitis	More common with increasing age	Small vessels	Necrotizing granulomatous inflammation	Affects the upper and lower respiratory tract; necrotizing glomerulonephritis is common; associated with PR3-ANCAs
Microscopic polyangiitis	More common with increasing age	Small vessels	Necrotizing vasculitis with few or no immune deposits and no granulomata	Necrotizing glomerulonephritis is very common; pulmonary capillaritis often occurs; associated with MPO-ANCAs
Eosinophilic granulomatosis with polyangiitis	More common with increasing age	Small to medium vessels	Eosinophil-rich and necrotizing granulomatous inflammation	Affects the respiratory tract and is associated with asthma and eosinophilia; ANCAs are more frequent when glomerulonephritis is present
IgA vasculitis	<16 years	Predominantly capillaries, venules or arterioles	Vasculitis with IgA1-dominant immune deposits	Often involves skin, joints and gastrointestinal tract; glomerulonephritis indistinguishable from IgA nephropathy can occur
Hypocomplementaemic urticarial vasculitis	40–60 years	Predominantly capillaries, venules or arterioles	Vasculitis	Urticaria, glomerulonephritis, arthritis, obstructive pulmonary disease and ocular inflammation are common; anti-C1q antibodies are present
Other				
Behçet syndrome	More common during the second and third decades	Aorta, arteries and veins of all sizes, including cerebral venous sinuses	Non-granulomatous, predominantly neutrophilic inflammation	Oral and genital ulcers, papulopustular and erythema nodosum-like lesions, arthritis, uveitis and vascular involvement; central nervous system and gastrointestinal system involvement is less frequent

ANCA, antineutrophil cytoplasmic antibody; C1q, complement protein C1q; HBV, hepatitis B virus; MPO, myeloperoxidase; PR3, proteinase 3.

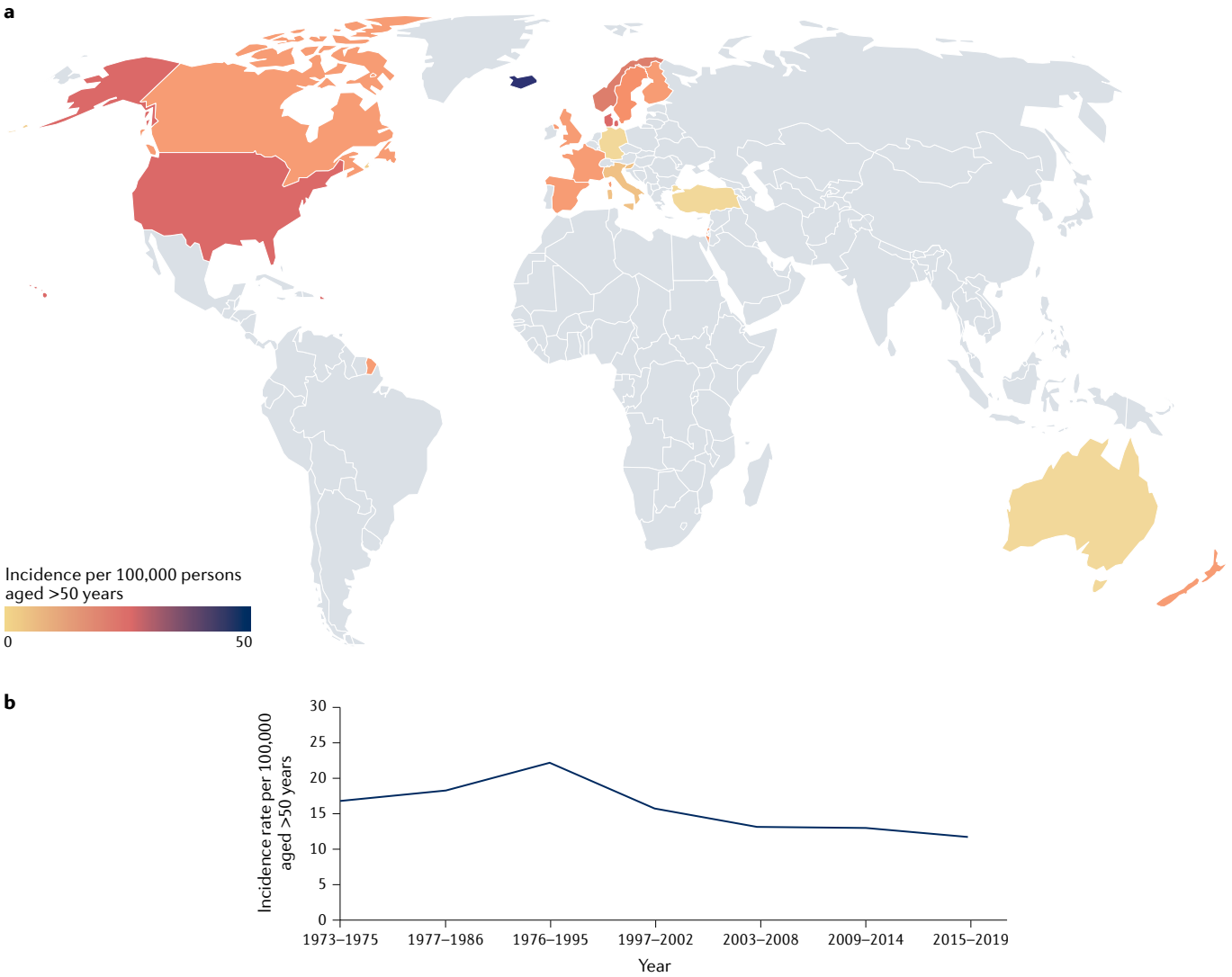


Fig. 1 | **Global incidence of giant cell arteritis. a** | Giant cell arteritis occurs most frequently in populations of Northern European ancestry. See Supplementary Table 1 for data used. Grey indicates no data available. **b** | Changing incidence of giant cell arteritis. Giant cell arteritis is gradually becoming less common, having peaked in incidence around 1990. Data from REFS[34,38–40].

of TAB-confirmed GCA might be decreasing. Several long-term studies have now reported data from the same population over 40 years[34,38–40]. FIGURE 1b illustrates changes in the incidence rate of TAB-confirmed GCA over 40 years in two Swedish regions with comparable populations that used similar case identification. The incidence rate of TAB-proven GCA in Sweden during 1976–1995 was 22.2 per 100,000 inhabitants aged ≥50, decreasing to 13.3 per 100,000 during 1997–2019, and there was a simultaneous decrease in the rate at which TAB was performed, from 74.1 per 100,000 (95% CI 70.7–77.5) during 1997–2002 to 50.2 per 100,000 (95% CI 47.4–53.0) during 2015–2019 (REFS[34,40]). The decreases in the rate of performing TABs and in the incidence of TAB-proven GCA might be explained by the increasing use of imaging studies in place of TAB and the changing demographics of Sweden, as immigration from areas with a lower prevalence of GCA has increased.

A striking feature of the epidemiology of GCA is the strong effect of age. For example, in a well-documented population in Sweden, the incidence rate was 2.0 per 100,000 in those aged 50–60 years and 31.3 per 100,000 in those aged 71–80 years[41]. Data suggest that there might be a decline in incidence in those aged >90 years, which could reflect underdiagnosis in this age group[41]. The mean age at diagnosis of GCA increased by 4.5 years between 1997 and 2010, mainly as a result of increased incidence in people aged 70 years and older, findings that might indicate interactions between environmental factors and an ageing immune system[42]. In addition, numerous studies have shown that GCA is 2–3 times more common in women than men in all age groups[37] (Supplementary Table 1).

The aetiology of GCA is poorly understood, but associations with host and environmental factors have been investigated. Obesity and diabetes mellitus are negatively associated with GCA[43–45], whereas exposure

to different infections, particularly those that affect the respiratory system, is associated with an increased risk of GCA[46,47]. Studies on smoking have shown variable effects that range from a protective effect on GCA development in men to an association with increased risk of GCA in women[48,49]. The effect of seasonality on GCA onset has also produced conflicting data: some studies have shown increasing occurrence during summer[50–52] or spring and summer[40], whereas a large study that included >2,200 patients with GCA from Australia, New Zealand, Germany and the Netherlands showed an even distribution of GCA diagnosis throughout the year[53].

Compared with incidence studies, few studies on the prevalence of GCA have been published. This paucity of data is probably due to the nature of the disease, as many patients achieve long-term remission off treatment and are therefore not included in prevalence estimates. Similar to incidence estimates, different criteria and case definitions, as well as different epidemiological definitions, are used for prevalence studies, which either report point prevalence or cumulative prevalence. In general, more recent studies have reported higher prevalence figures than older studies. For example, in the UK, a cumulative prevalence of 250 per 100,000 was reported in 2016 using data from a primary care setting[54]; however, these results were based on a single general practice, and a UK study from the 1990s reported a prevalence of 84 per 100,000 (REF.[55]). In North America, data from Olmsted County, MN, USA suggest a prevalence of 204 per 100,000 in 2015 (REF.[56]), whereas in Ontario, Canada, the prevalence in 2018 was 235 per 100,000, compared with 125 per 100,000 in 2000 (REF.[57]). A Swedish study from 2021, in which treatment with glucocorticoids on the date of prevalence calculation was required for inclusion, reported an overall prevalence of 75.5 per 100,000 (107.8 per 100,000 in women and 40.1 per 100,000 in men)[40]. The prevalence of GCA in the same population irrespective of steroid treatment was 127.1 per 100,000. The higher figure reflects inclusion of patients with polymyalgia rheumatica who had ever been treated with steroids. By contrast, a very low prevalence rate of 1.47 per 100,000 was reported in a study from Japan in the 1990s[58]. Interestingly, unlike the association between incidence of GCA and latitude, a 2021 meta-analysis did not demonstrate an association between latitude and GCA prevalence[29]. This discrepancy between incidence and prevalence in the meta-analysis probably reflects the relative paucity of prevalence studies.

Medium vessel vasculitis

Polyarteritis nodosa. Polyarteritis nodosa is a systemic necrotizing vasculitis that predominantly affects medium-sized muscular arteries[3]. Hepatitis B virus (HBV) is a well-recognized trigger infection for polyarteritis nodosa, and HBV-associated polyarteritis nodosa is now classified as a separate disease. With the introduction of widespread vaccination against HBV, there has been a reduction in the proportion of patients with polyarteritis nodosa who are infected with HBV[59]. Polyarteritis nodosa is estimated to have an annual incidence rate of 0.9–8.0 per million in European countries[60,61], and a prevalence of 31 per million[59,62]. Polyarteritis nodosa can affect patients of all ethnicities, typically occurs in patients aged 40–60 years and, unlike most other types of vasculitis, has a male preponderance (male-to-female ratio of 1.5:1)[59]. In addition, polyarteritis nodosa can occur in association with familial Mediterranean fever[63].

Kawasaki disease. Kawasaki disease differs in important ways from the other forms of vasculitis covered in this Review. Kawasaki disease almost exclusively affects children (85% of affected patients are under the age of 5 years[64]), and the vasculitis is self-limited, with all patients seeming to completely recover. Another difference is that the systemic inflammation during the acute phase of the illness is not confined to the arterial wall but also affects the myocardium; myocarditis by histological criteria is a universal finding during acute illness[65,66]. Decades later, autopsy studies of patients with giant aneurysms who had previously had Kawasaki disease show diffuse, bridging fibrosis beyond the territories supplied by the affected arteries[67,68]. The genesis of this fibrosis is uncertain but it could be the result of subclinical, smouldering microvascular inflammation or of chronic myocardial inflammation. Another unique feature of Kawasaki disease is its emergence as a new condition in Asia after World War II[69,70]. The existence of Kawasaki disease in North America in the nineteenth and early twentieth centuries as a rare, uniformly fatal condition called infantile polyarteritis nodosa is supported by comparison of autopsies of patients with infantile polyarteritis nodosa and those with Kawasaki disease[71].

The epidemiology of Kawasaki disease is an imprecise science as there is no specific diagnostic test for the condition. Kawasaki disease is diagnosed on the basis of clinical criteria coupled with laboratory evidence of acute inflammation with or without dilation of the coronary arteries by transthoracic echocardiography. Infants and children present with fever and mucocutaneous manifestations including conjunctival injection, rash, erythema of the oral mucosa and vermillion border, cervical lymphadenopathy and swelling of the dorsa of the hands and feet[72]. Without treatment, 25% of children will develop coronary artery aneurysms that can lead to thrombosis, myocardial infarction, heart failure or death[73]. Treatment with intravenous immunoglobulin as an immunomodulatory agent reduces the incidence of aneurysms to 3–5%[74].

Kawasaki disease has been reported in more than 60 regions spanning five continents[75]. The epidemiology of Kawasaki disease has been most clearly defined for Japan, the location with the highest known incidence in the world, where questionnaire surveys of hospitals with at least 100 beds have been conducted every 2 years since 1970 (REF.[76]). Nationwide epidemics of Kawasaki disease in Japan in 1979, 1982 and 1986 were followed by steadily increasing numbers of cases, leading to the current incidence rate of 359 per 100,000 children <5 years of age. According to the latest estimates from Japan, approximately 1 in every 64 boys and 1 in every 80 girls will develop Kawasaki disease during the first 10 years of their life[77]. A genetic predisposition to Kawasaki disease is supported by its occurrence in first-degree relatives

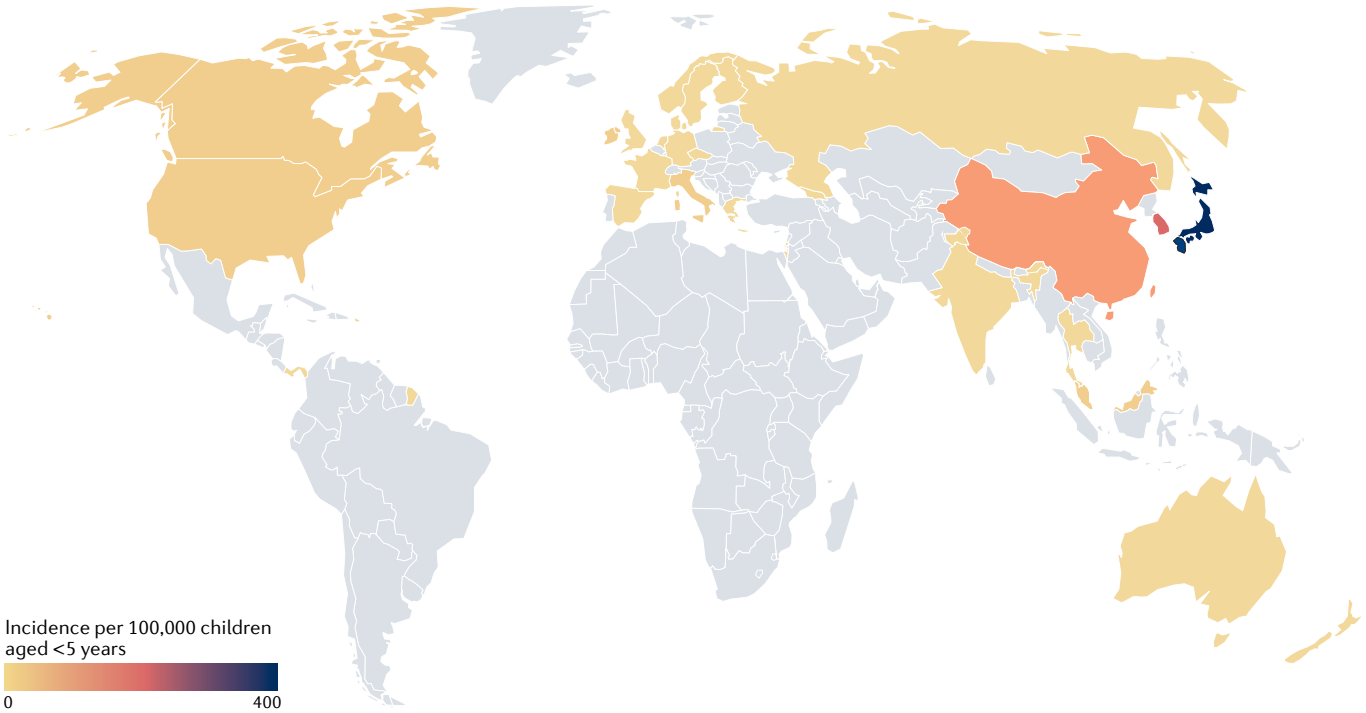
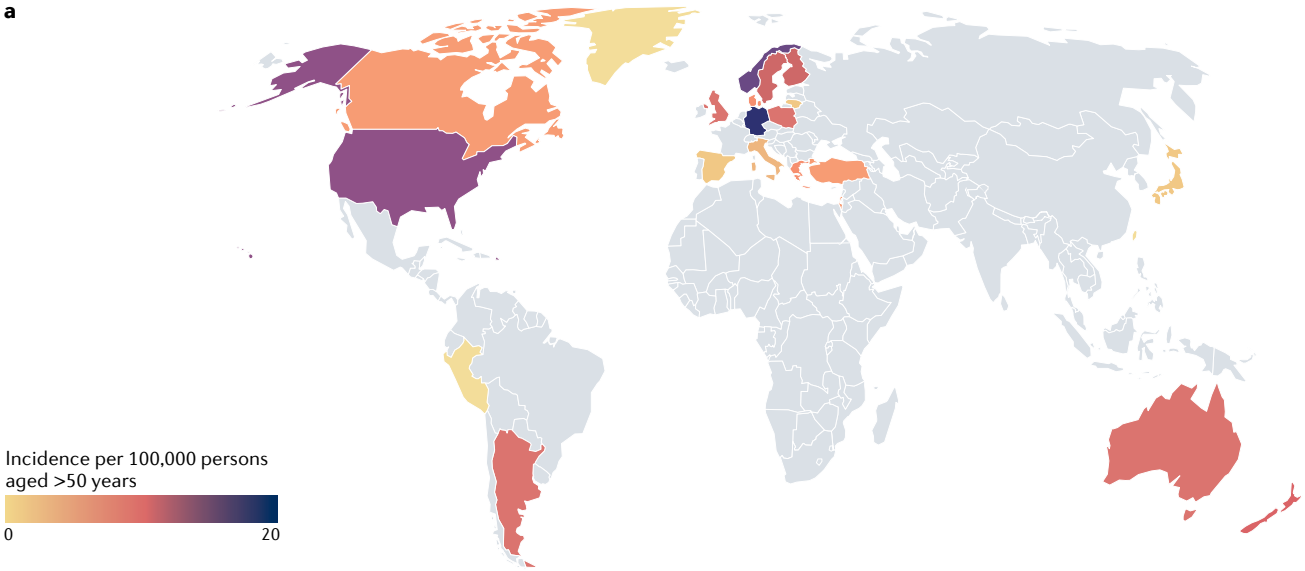


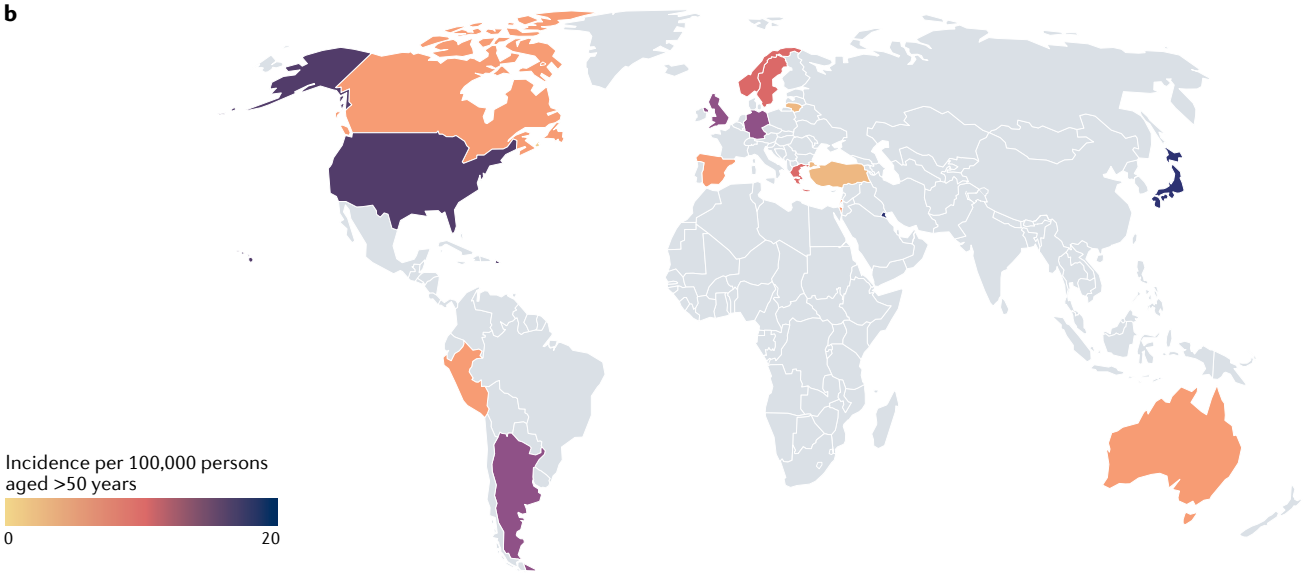
Fig. 2 | **Global incidence of Kawasaki disease.** Kawasaki disease occurs most frequently in East Asia, especially Japan, South Korea and China, with a relatively equal distribution elsewhere. See Supplementary Table 2 for data used. Grey indicates no data available.

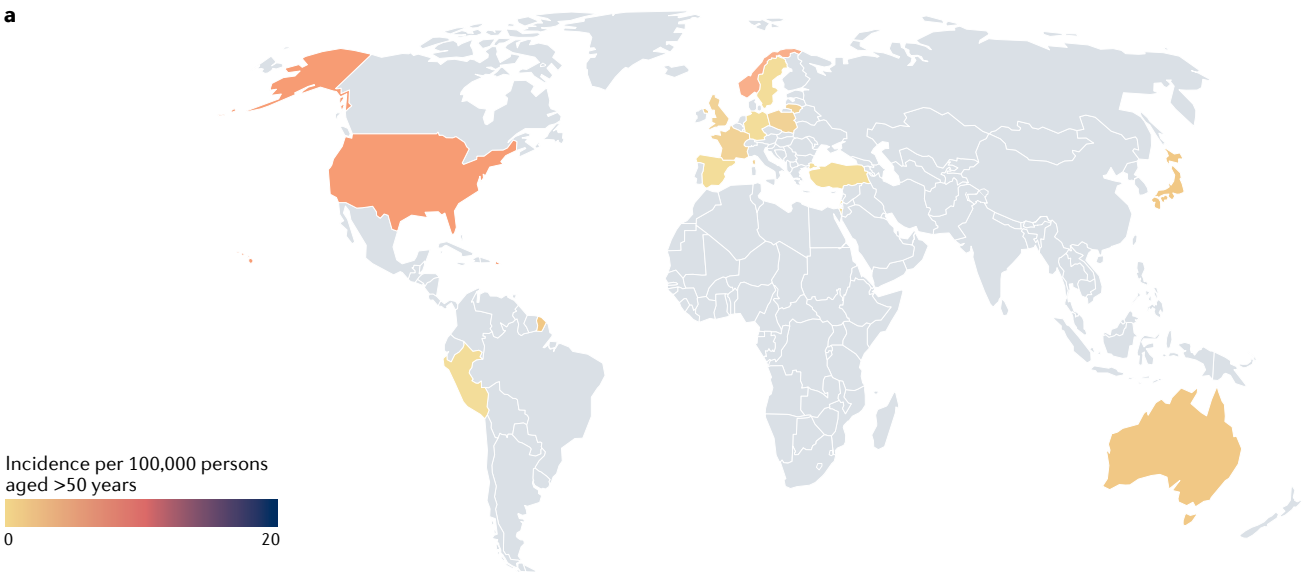
of patients with the disease, the increased incidence of Kawasaki disease in children of Asian descent living outside of Asia, and the discovery of genetic variants that influence susceptibility[78]. The incidence of Kawasaki disease is high throughout Northeast Asia, with incidence rates per 100,000 children <5 years of 195 in South Korea and 60 in Taiwan[79,80] (FIG. 2, Supplementary Table 2). Both of these regions have national health systems and nationwide databases that permit accurate tracking of disease incidence. In other parts of Asia, the lack of accurate population statistics and a centralized database has resulted in uncertainty regarding the incidence of Kawasaki disease. For example, in India and China, the two most populous regions of the world, there is no centralized collection of data to aid in disease epidemiology. The epidemiology of Kawasaki disease in China and India has been fully reviewed elsewhere[81]. Briefly, questionnaire-based studies from Beijing and Shanghai have reported incidence rates of 46.3–55.1 per 100,000 children aged <5 years. The emergence of Kawasaki disease in India is thought to be a recent occurrence and case numbers have been steadily rising, although there is a debate as to whether this is due to increased case ascertainment or a true rising incidence[82]. Increased recognition of Kawasaki disease might also be due to a reduction in vaccine-preventable diseases that manifest with rash and fever, and which can mimic the clinical features of Kawasaki disease[83]. Only regional incidence rates are available for India. In Chandigarh in northern India, incidence rates from 2009–2014 have varied between 1 per 100,000 and 9 per 100,000 children aged <5 years[84].

European and North American locations with national health services and centralized data collection have reported incidence rates per 100,000 in children aged <5 years that range from 19.6 in Canada to 4.5–9.0 in the UK and most of Europe[85–88]. Low rates have also been reported in Finland, Sweden and Norway (11.4, 5.4 and 7.4 per 100,000 children aged <5 years, respectively)[89]. In the USA, administrative databases have been used to estimate the burden of disease. Using such databases, estimated incidence rates for Kawasaki disease are approximately 20 per 100,000 children aged <5 years[90]. Prospective epidemiological investigation over a 10-year period from a region in southern California with a large Hispanic population revealed incidence rates per 100,000 children aged <5 years of 14.9, 20 and 50 for children of European, Hispanic and Asian or Pacific Islander descent, respectively[64].

Intriguing aspects of Kawasaki disease epidemiology include the distinct global seasonality, with peaks in winter, spring and mid-summer, and the temporal and spatial clustering of cases[91–94]. No evidence exists to support person-to-person transmission of Kawasaki disease, and clinical features, including cervical lymphadenopathy, hoarseness and retropharyngeal oedema, all suggest a respiratory point of entry[95–97]. Potential clues to the aetiology of Kawasaki disease can be gleaned from the analysis of temporal clusters that share distinct clinical and laboratory features. The existence of these sub-phenotypes suggests that Kawasaki disease might be triggered by diverse agents that each yield slight variations in clinical presentation[98]. A surprising observation from the past year is the large decrease in the incidence of Kawasaki disease in Japan and the USA during the SARS-CoV-2 pandemic, which supports the hypothesis that Kawasaki disease is triggered by inhaled aerosols


a
Incidence per 100,000 persons aged >50 years
0
20


b
Incidence per 100,000 persons aged >50 years
0
20


a
Incidence per 100,000 persons aged >50 years
0
20

◀ Fig. 3 | **Global incidence of ANCA-associated vasculitis.** Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis subtypes show different patterns of occurrence across populations. For example, in Southern Europe and Japan, microscopic polyangiitis is more common than granulomatosis with polyangiitis, whereas as in most other populations, granulomatosis with polyangiitis is the more common form. Eosinophilic granulomatosis with polyangiitis is the least common of the three conditions. See Supplementary Table 3 for data used. Grey indicates no data available. **a** | The global incidence of granulomatosis with polyangiitis. **b** | The global incidence of microscopic polyangiitis. **c** | The global incidence of eosinophilic granulomatosis with polyangiitis.

that can be blocked or reduced by the use of facial masking[99,100]. The possibility of long-range transport of aerosols linked to fluctuations in Kawasaki disease incidence has been studied in both Northern and Southern Hemispheres[93,101,102]. Atmospheric circulation patterns have been reported that link winds from northeastern China with fluctuations in incidence rates of Kawasaki disease in Japan and winds from the Atacama Desert with Kawasaki disease incidence in southern Chile[102,103]. At least in Northeast Asia, exposure to the causative agents of Kawasaki disease continues to increase and case numbers continue to steadily climb[104].

Small vessel vasculitis

ANCA-associated vasculitis. AAV is a group of three conditions predominantly affecting small vessels, the main types being granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA)[3] (TABLE 1). The incidence of AAV has increased during the past 40 years. The combined incidence rate for GPA, MPA and EGPA from Norway (1999–2013) and the USA (1996–2015) was around 24.7 per million in Norway[105] and 33.0 per million in the USA[106], compared with a rate of only 1.5 per million for GPA alone in the UK in the 1980s[107]. FIGURE 3 and Supplementary Table 3 summarize the incidence rates of AAV around the globe since 2000. The increased reported incidence is attributable to improved case recognition following the widespread introduction of ANCA testing in the 1990s and the application of uniform, albeit imperfect, classification criteria. The widespread adoption of the 1994 Chapel Hill Consensus definitions for vasculitis resulted in the recognition of MPA as an entity distinct from polyarteritis nodosa[6]. With the acknowledged imperfections of the ACR and Chapel Hill Consensus criteria for classification, there has been debate as to whether it is preferable to classify patients by ANCA serotype (proteinase 3 and myeloperoxidase (MPO)) alone rather than by the clinical phenotype[108]. It is hoped that the new EULAR–ACR classification system, which incorporates ANCA status, will help to resolve this debate[8–10].

In the most recent study from northern Norway, the incidence rate for MPA substantially increased from 2.7 per million in 1999–2003, to 10.4 per million in 2009–2013 (REF.[105]). A study using data from the 1980s and 1990s in which the incidences of GPA and MPA were compared across Europe suggested that GPA was more common than MPA in Northern Europe, whereas the opposite was true in Southern Europe[109]. However, data from the late 1990s and 2000s from several European countries have suggested that this might no longer be true[61,110,111]. Data from epidemiological studies, serological studies and large case series suggest that MPA is much more common than GPA in China and Japan[112,113]. To confirm these observations, it will be critical to rigorously classify cases using the same criteria. Moreover, separating the influence of genetic and environmental factors in such studies will be difficult, as people with different genetic backgrounds have been studied in different geographical locations, limiting comparison. A global study reported that MPO-ANCA was much more common in Japanese, Chinese and Southern European individuals than in Northern European individuals[114]. In the same study, ophthalmological and ear, nose and throat involvement was less common in Japanese and Chinese patients with AAV than in Northern European patients with AAV. In a multi-ethnic series from Chapel Hill in the USA, GPA was less common in African American individuals than in those with European ancestry[115]. By contrast, in the UK, there was no evidence of an effect of ethnicity on the occurrence of GPA in a combined primary and secondary database study[116]. In all countries studied so far, EGPA is the rarest of the three forms of AAV, with an incidence rate in the range 0.14–4.0 per million and no evidence of a change over time (Supplementary Table 3).

In addition to the increasing incidence of AAV, there has also been an increase in the peak age at diagnosis. In studies looking at data from the late twentieth century, the peak age-specific incidence was reported in those aged 65–74 years in the UK and Finland[60,117]. In data from the early twenty-first century in the UK, the peak age for AAV incidence had increased to >80 years[116]. Again, the reasons for the increased diagnosis of AAV in older individuals are not clear, but could be related to the increasing ease of ANCA testing, which might lead to the identification of patients who would not previously have been considered to have AAV. At the other end of the age spectrum, AAV is very uncommon. The incidence rate of AAV in those aged 0–17 years is 0.45 per million in France[118] and 3.2 per million in Sweden[119]. Overall, AAV is slightly more common in men than in women (male-to-female ratio of between 1.07:1 and 1.48:1)[110,111,120,121].

The trigger for development of AAV is unknown, and environmental factors have been extensively investigated[122]. Some studies have reported a cyclical pattern of incidence suggestive of an infectious trigger but, so far, no clear infectious trigger has been identified for AAV[123,124]. Seasonality has also been investigated as a clue to infection; however, no clear pattern has been observed. European studies from the 1990s suggested a trend towards an increase in GPA in the winter[123,125], whereas more recent studies have suggested a summer link or no association[126,127], which might reflect differences in case definition by date of symptom onset or date of diagnosis. A study looking at health-care events occurring prior to a diagnosis of GPA in a UK general practice database did not report any health events that predicted subsequent development of vasculitis[128]. Silica has also been proposed as a possible trigger in a number of small studies[129] and, in 2021, a geospatial association was reported between GPA and quarries in the Alsace region of France[130]. Other

reported risk factors include rural living and farming[131,132]. Social factors have also been investigated, but no clear association with socio-economic status has so far been demonstrated, possibly reflecting differences in case definition (such as renal versus non-renal vasculitis) and assessment of socioeconomic status[127].

Compared with incidence studies, there are relatively fewer studies on the prevalence of AAV. Prevalence rates for GPA as high as 261.0 per million have been reported in Norway, with rates of 58.2 per million for MPA and 32.9 per million for EGPA[105]. The prevalence of AAV has increased owing to a combination of increasing incidence, improved case definitions, the emergence of a number of local or national vasculitis registries in different locations around the world and improved survival as a result of improvements in treatment.

IgA vasculitis. IgA vasculitis (previously known as Henoch–Schönlein purpura) is an immune complex vasculitis that predominantly affects small vessels[3]. In children and adolescents, IgA vasculitis is the most common type of vasculitis, the main features being cutaneous palpable purpura, arthralgia or arthritis, bowel angina, and haematuria or proteinuria[119,133]. The annual incidence rate of IgA vasculitis is between 3.5 (in Japan) and 26.7 (in Scotland) per 100,000 persons aged <15 years[134,135], and the highest rate reported is between the ages of 4 and 6 years (70.3 per 100,000 in the UK)[119,133]. European studies have reported an incidence in Sweden (2004–2014) of 17.5 per 100,000 persons aged <15 years and in France (2012–2014) of 18.6 per 100,000 persons aged <15 years[11,119]. A study in a multi-ethnic cohort from Birmingham, UK, reported that IgA vasculitis was more common in those of Indian subcontinent ancestry (24.0 per 100,000 persons aged <17 years) than in white individuals (17.8 per 100,000 persons <17 years) or Black individuals (predominantly those of Afro-Caribbean ancestry; 6.2 per 100,000 persons aged <17 years)[133]. A 2017 study from France similarly noted an increased occurrence of IgA vasculitis in children of North African ancestry[11].

In adults, IgA vasculitis is much less common than in children, with a broad range of incidence estimates. Studies suggest that the incidence in Spain between 1992 and 2010 was 1.5 per million and in Finland (2010) it was 15 per million, although the latter figure is based on two cases[136,137]. The mean age of onset for IgA vasculitis in adults is 50 years, and the condition is more common in men than in women[138]. IgA vasculitis is typically a disease with a relatively short duration and there are few data on prevalence, although a study from Spain has reported a prevalence of 7.9 per million[136].

Hypocomplementaemic urticarial vasculitis. Hypocomplementaemic urticarial vasculitis is a form of vasculitis characterized by urticaria and hypocomplementaemia and is associated with anti-C1q antibodies[3]. Only a single study exists that describes the epidemiology of hypocomplementaemic urticarial vasculitis. A small Swedish study reported an annual incidence rate of 0.7 per million persons with a point prevalence on 31 December 2015 of 9.5 per million[139]. The median age of onset was 51 years and 87.5% of patients were women.

Behçet syndrome

Behçet syndrome is a variable vessel vasculitis that runs a remitting and relapsing course with oral and genital ulcers, erythema nodosum-like and papulopustular skin lesions, arthritis, uveitis, arterial aneurysms, arterial and venous thrombosis, parenchymal nervous system lesions and intestinal ulcers[3]. Formal incidence studies are rare for Behçet syndrome. Annual incidence rates have been reported from South Korea (3.9 per 100,000), Taiwan (2.4 per 100,000), Poland (0.05 per 100,000) and Sweden (0.2 per 100,000)[140–143]. By contrast, the prevalence of Behçet syndrome has been widely studied and shows substantial variability between countries[12,140–142,144–154] (FIG. 4 and Supplementary Table 4). The highest burden is documented along the ancient silk road, which runs from the eastern Mediterranean and the Middle East to East Asia, with estimated prevalence rates of 421 per 100,000 in Turkey, 660 per 100,000 in Jordan, 100 per 100,000 in Iran, 35.0 per 100,000 in South Korea, 13.5 per 100,000 in Japan and 10.0 per 100,000 in China[147,149–152,154]. In the USA, studies have reported estimated prevalence rates of between 0.33 and 10.6 per 100,000 and in South America, rates of 0.3 per 100,000 have been reported in Brazil and 1.1 per 100,000 in Colombia[144–146,153]. A 2018 meta-analysis showed that pooled estimates of prevalence proportions were 10.3 per 100,000 for all studies included, and 31.8 per 100,000 for the Middle East, 4.5 per 100,000 for Asia and 3.3 per 100,000 for Europe[12]. The prevalence tends to decrease towards the north in Europe and towards the south in Africa. Differences in study design, calculating prevalence rates versus prevalence odds ratios and the criteria used for case ascertainment make it difficult to compare prevalence studies from different countries. Notably, in the meta-analysis, population-based studies showed a 12-fold higher prevalence than hospital or registry-based studies in the same geographic area[12].

Similar to disease prevalence, disease severity and the occurrence of specific manifestations in Behçet syndrome, as well as the association with HLA-B51 positivity, also show geographical variation. The risk of developing Behçet syndrome is increased by a factor of 5.78 for carriers of *HLA-B51* or *HLA-B5* (REF.[155]), and the prevalence of Behçet syndrome in a population is generally positively associated with the prevalence of HLA-B51. For example, a study from Turkey showed that 30% of the general population were positive for HLA-B51 and Behçet syndrome had a prevalence of 421.0 per 100,000 (REF.[149]). By contrast, a study showed that 8.9% of the general population was HLA-B51 positive in the UK[156], where the prevalence of Behçet syndrome is 14.6 per 100,000 (REF.[157]). An exception to this rule is some Native American populations in southwestern USA, in which HLA-B51 is common but the prevalence of Behçet syndrome is low[144].

Behçet syndrome occurs at a similar rate in both men and women, but a more severe prognosis, more organ involvement and higher mortality rates are reported among men[158]. Behçet syndrome usually starts during the second or third decade of life, and an early age of disease onset seems to be a poor prognostic factor in addition to male sex[159]. Despite differences between

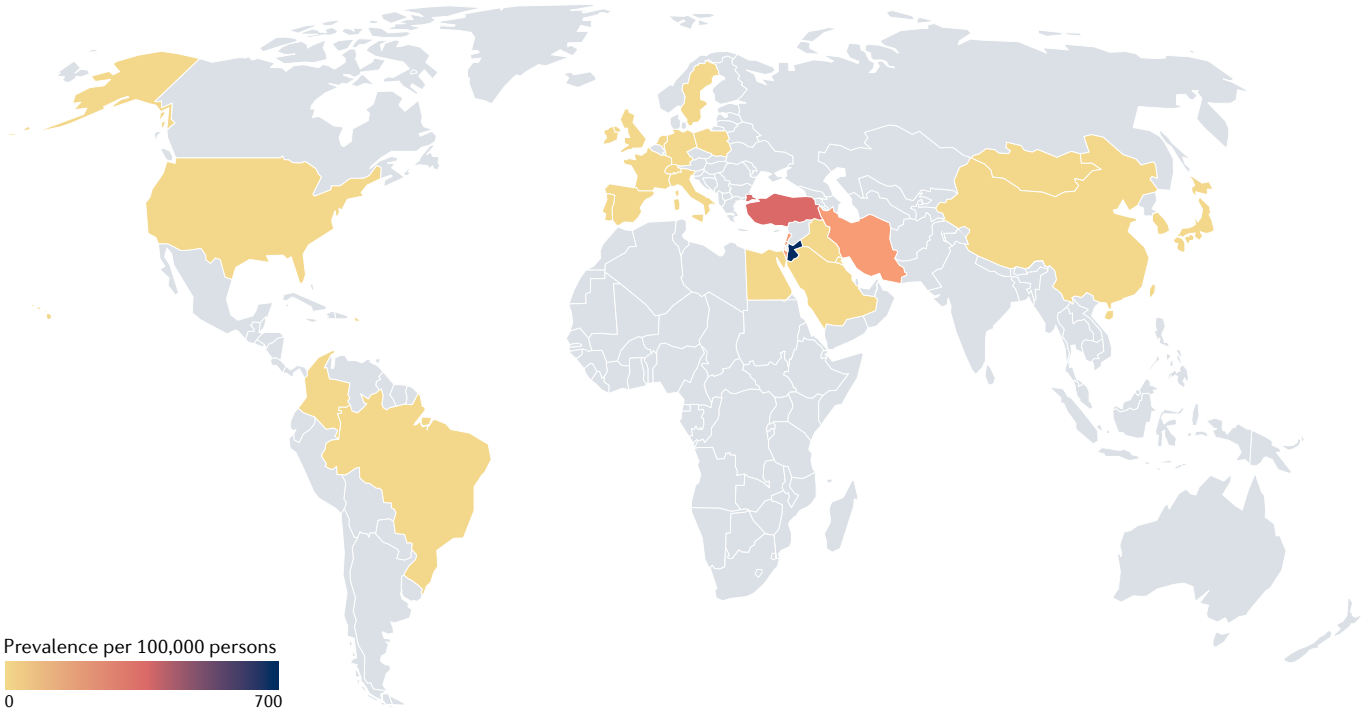


Fig. 4 | **Global prevalence of Behçet syndrome.** Behçet syndrome occurs most commonly along the ancient silk road between the Mediterranean and China. See Supplementary Table 4 for data used. Grey indicates no data available.

cohorts, in general, women more commonly have isolated skin, mucosal and musculoskeletal involvement, whereas men more commonly have uveitis, vascular and, in some series, central nervous system involvement[158]. Differences have also been observed in how common certain manifestations are among geographical locations. Gastrointestinal involvement was reported in up to 30% of patients in East Asia and the USA, compared with around 1% in Turkey, Tunisia and Spain[148]. A positive reaction to the pathergy test (hyperreactivity of the skin to a needle prick) is more common in the Mediterranean region and East Asia, whereas it is much less common in Northern Europe[148,160]. A number of studies that compared patients with Behçet syndrome in the USA with those in other countries showed more women, more gastrointestinal and nervous system involvement, higher disease activity and worse quality of life in patients in the USA than patients in Turkey[161]; more genital ulcers, less epididymitis and pulmonary involvement than patients in Japan[162]; and more women, earlier age of onset, more genital ulcers, skin lesions, arthritis, nervous system and cardiovascular involvement than patients in Iran[163]. The general contention has been that Behçet syndrome runs a more severe course in countries with a high prevalence. Although the results of these studies run contrary to that presumption, it is thought that the reports of more severe disease in the USA might be associated with the fact that only those patients with more severe disease are referred and diagnosed in the USA.

A number of studies have looked at the change in the prevalence, severity and occurrence of disease manifestations of Behçet syndrome over time, with varying results. A study from Japan reported a decrease in Behçet syndrome prevalence over decades, whereas a South Korean study reported a small, but steady increase[152,164]. By contrast, a more recent study from South Korea suggested that there had been a substantial decline in the incidence of Behçet syndrome[165]. Overall, a milder disease course has been reported in different studies, with fewer skin lesions, genital ulcers and positive pathergy tests, and a decrease in the occurrence and severity of uveitis[164,166,167]. One of the hypotheses for explaining the milder disease course was the possibility of improved living conditions and hygiene, as an association with infections has been proposed in the pathogenesis of Behçet syndrome. Although infections have been considered to be the main environmental trigger, no solid evidence exists to support a link with any specific microorganism[168]. Some dysbiosis has been noted in all microbiota studies in Behçet syndrome, but which microorganisms were abundant or decreased differed in studies from different regions. Interestingly, an increase in the occurrence of gastrointestinal involvement has been reported in both Japan and South Korea[164,167]. Notably, an increase in the prevalence of inflammatory bowel diseases has also been reported in East Asia, which was attributed to the adoption of a Western diet[169,170]. Therefore, it is not clear whether a similar association might also be true for gastrointestinal involvement of Behçet syndrome, which highly resembles Crohn's disease.

By contrast, an increase in the prevalence of Behçet syndrome over time has been reported in Europe, including in the UK, Ireland and Sweden[143,157,171]. Increased awareness among physicians and changes in the disease criteria that were used have been considered as possible explanations for this increase, as well as immigration from regions with a high prevalence of Behçet syndrome. Studies comparing the prevalence and disease

characteristics of Behçet syndrome among immigrants and locals in Europe have provided important clues to our understanding of Behçet syndrome regarding the roles of genetic and environmental factors. Such studies from Germany, France, Italy, Switzerland, Sweden and the Netherlands reported that the prevalence of Behçet syndrome among immigrants was higher than the prevalence among locals, and was somewhat lower than or similar to the prevalence in the immigrant's region of origin[143,172–176]. These results were thought to support the role of both genetics and the environment in the pathogenesis of Behçet syndrome, but could be biased by differences in living conditions and health-care access between people of different ethnicities within the same geographic area. Moreover, the association with age at immigration and prevalence among second-generation and third-generation immigrants have not been adequately studied.

Conclusions

In conclusion, knowledge of the epidemiology of vasculitis has increased over the past two decades, and it has become apparent that vasculitis occurs most commonly at the ends of the age spectrum. Kawasaki disease is predominantly a disease of those aged under 5 years and IgA vasculitis is predominantly a disease of childhood and adolescence, suggesting a role for infection in the initiation of vascular inflammation in these conditions. By contrast, GCA is a disease of older individuals, being the most common type of vasculitis in those aged over 65 years, perhaps pointing to an interaction between infection and the ageing immune system. Although much less common than GCA, AAV also shows an increasing incidence with age. The underlying triggering factors for most forms of vasculitis remain broadly unknown, although some clues are emerging in relation to infection, the role of the environment (such as links between certain minerals and AAV) and genetics. However, considerable lacunae remain in our knowledge of the basic descriptive epidemiology of vasculitis. Very few high-quality data exist from the two most populous regions of the planet, and the effects of ethnic background, together with other social factors including deprivation, are largely unknown. Future research should address the urgent need for a global dataset to describe the occurrence of disease, variations in which both temporally and geographically might provide insights into pathogenesis. Better global prevalence data will enable the disease burden to be estimated, which is important as vasculitis is associated with substantial long-term morbidity, including vision loss in GCA, coronary artery aneurysms in Kawasaki disease and renal failure in AAV. These long-term morbidities are associated with considerable costs, both financial to health services and society, and to individuals.

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1. Newburger, J. W., Takahashi, M. & Burns, J. C. Kawasaki disease. *J. Am. Coll. Cardiol.* **67**, 1738–1749 (2016).
2. Akiyama, M. et al. Innate and adaptive immunity in giant cell arteritis. *Front. Immunol.* **11**, 621098 (2020).
3. Jennette, J. et al. 2012 revised international Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum.* **65**, 1–11 (2013).
4. Fries, J. F. et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. *Arthritis Rheum.* **33**, 1135–1136 (1990).
5. Seeliger, B. et al. Are the 1990 American College of Rheumatology vasculitis classification criteria still valid? *Rheumatology* **56**, 1154–1161 (2017).
6. Jennette, J. C. et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum.* **37**, 187–192 (1994).
7. Craven, A. et al. ACR/EULAR-endorsed study to develop diagnostic and classification criteria for vasculitis (DCVAS). *Clin. Exp. Nephrol.* **17**, 619–621 (2013).
8. Grayson, P. et al. 2021 American College of Rheumatology/European League Against Rheumatism classification criteria for eosinophilic granulomatosis with polyangiitis. *Ann. Rheum. Dis.* (in the press) (2021).
9. Suppiah, R. et al. 2021 American College of Rheumatology/European League Against Rheumatism classification criteria for microscopic polyangiitis. *Ann. Rheum. Dis.* (in the press) (2021).
10. Robson, J. et al. 2021 American College of Rheumatology/European League Against Rheumatism classification criteria for granulomatosis with polyangiitis. *Ann. Rheum. Dis.* (in the press) (2021).
11. Piram, M. et al. Incidence of IgA vasculitis in children estimated by four-source capture — recapture analysis: a population-based study. *Rheumatology* **56**, 1358–1366 (2017).
12. Maldini, C., Druce, K., Basu, N., LaValley, M. P. & Mahr, A. Exploring the variability in Behçet's disease prevalence: a meta-analytical approach. *Rheumatology* **57**, 185–195 (2018).
13. Maksimowicz-McKinnon, K., Clark, T. M. & Hoffman, G. S. Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? *Medicine* **88**, 221–226 (2009).
14. Arend, W. P. et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum.* **33**, 1129–1134 (1990).
15. Hunder, G. G. et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* **33**, 1122–1128 (1990).
16. Gribbons, K. B. et al. Patterns of arterial disease in Takayasu arteritis and giant cell arteritis. *Arthritis Care Res.* **72**, 1615–1624 (2020).
17. Watts, R., Al-Taiar, A., Mooney, J., Scott, D. & Macgregor, A. The epidemiology of Takayasu arteritis in the UK. *Rheumatology* **48**, 1008–1011 (2009).
18. Gudbrandsson, B., Molberg, Ø., Garen, T. & Palm, Ø. Prevalence, incidence and disease characteristics of Takayasu arteritis differ by ethnic background; data from a large, population based cohort resident in southern Norway. *Arthritis Care Res.* **69**, 278–285 (2017).
19. Mohammad, A. J. & Mandl, T. Takayasu arteritis in southern Sweden. *J. Rheumatol.* **42**, 853–858 (2015).
20. Kanecki, K. et al. Takayasu's arteritis: a rare disease in Poland. *Ann. Agric. Environ. Med.* **25**, 469–472 (2018).
21. Park, S. J. et al. Incidence, prevalence, mortality and causes of death in Takayasu Arteritis in Korea — a nationwide, population-based study. *Int. J. Cardiol.* **235**, 100–104 (2017).
22. Koide, K. Takayasu arteritis in Japan. *Heart Vessels Suppl.* **7**, 48–54 (1992).
23. Rutter, M., Bowley, J., Lanyon, P. C., Grainge, M. J. & Pearce, F. A. A systematic review and meta-analysis of the incidence rate of Takayasu arteritis. *Rheumatology* **60**, 4982–4990 (2021).
24. Sanchez-Alvarez, C., Crowson, C. S., Koster, M. J. & Warrington, K. J. Prevalence of Takayasu arteritis: a population-based study. *J. Rheumatol.* **48**, 952 (2021).
25. Muratore, F. et al. Incidence and prevalence of large vessel vasculitis (giant cell arteritis and Takayasu arteritis) in northern Italy: a population-based study. *Semin. Arthritis Rheum.* **51**, 786–792 (2021).
26. Gloor, A. D. et al. Takayasu arteritis: prevalence and clinical presentation in Switzerland. *PLoS ONE* **16**, e0250025 (2021).
27. Terao, C., Yoshifuji, H. & Mimori, T. Recent advances in Takayasu arteritis. *Int. J. Rheum. Dis.* **17**, 238–247 (2014).
28. Saritas, F., Donmez, S., Direskeneli, H. & Pamuk, O. N. The epidemiology of Takayasu arteritis: a hospital-based study from northwestern part of Turkey. *Rheumatol. Int.* **36**, 911–916 (2016).
29. Li, K. J., Semenov, D., Turk, M. & Pope, J. A meta-analysis of the epidemiology of giant cell arteritis across time and space. *Arthritis Res. Ther.* **23**, 82 (2021).
30. Donaldson, L. & Margolin, E. Vision loss in giant cell arteritis. *Pract. Neurol.* https://doi.org/10.1136/practneurol-2021-002972 (2021).
31. Blockmans, D. et al. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum.* **55**, 131–137 (2006).
32. Gribbons, K. B. et al. Diagnostic assessment strategies and disease subsets in giant cell arteritis: data from an international observational cohort. *Arthritis Rheumatol.* **72**, 667–676 (2020).
33. Wiberg, F., Naderi, N., Mohammad, A. J. & Turesson, C. Evaluation of revised classification criteria for giant cell arteritis and its clinical phenotypes. *Rheumatology* https://doi.org/10.1093/rheumatology/keab353 (2021).
34. Petursdottir, V., Johansson, H., Nordborg, E. & Nordborg, C. The epidemiology of biopsy-positive giant cell arteritis: special reference to cyclic fluctuations. *Rheumatology* **38**, 1208–1212 (1999).
35. Salvarani, C., Crowson, C. S., O'Fallon, W. M., Hunder, G. G. & Gabriel, S. E. Reappraisal of the epidemiology of giant cell arteritis in Olmsted County, Minnesota, over a fifty-year period. *Arthritis Rheum.* **51**, 264–268 (2004).
36. Mackie, S. L. et al. Association of HLA-DRB1 amino acid residues with giant cell arteritis: genetic association study, meta-analysis and geo-epidemiological investigation. *Arthritis Res. Ther.* **17**, 195 (2015).
37. Sharma, A., Mohammad, A. J. & Turesson, C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: a systematic literature review. *Semin. Arthritis Rheum.* **50**, 1040–1048 (2020).
38. Bengtsson, B. A. & Malmvall, B. E. The epidemiology of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. Incidences of different clinical presentations and eye complications. *Arthritis Rheum.* **24**, 899–904 (1981).
39. Nordborg, E. & Bengtsson, B. A. Epidemiology of biopsy-proven giant cell arteritis (GCA). *J. Intern. Med.* **227**, 233–236 (1990).

40. Stamatis, P., Turkiewicz, A., Englund, M., Turesson, C. & Mohammad, A. J. Epidemiology of biopsy-confirmed giant cell arteritis in southern Sweden — an update on incidence and first prevalence estimate. *Rheumatology* https://doi.org/10.1093/rheumatology/keab269 (2021).
41. Mohammad, A. J., Nilsson, J.-Å., Jacobsson, L. T., Merkel, P. A. & Turesson, C. Incidence and mortality rates of biopsy-proven giant cell arteritis in southern Sweden. *Ann. Rheum. Dis.* **50**, 1040–1048 (2015).
42. Kermani, T. A. et al. Increase in age at onset of giant cell arteritis: a population-based study. *Ann. Rheum. Dis.* **69**, 780–781 (2010).
43. Ungprasert, P., Thongprayoon, C. & Warrington, K. J. Lower body mass index is associated with a higher risk of giant cell arteritis: a systematic review and meta-analysis. *Ann. Transl. Med.* **3**, 232 (2015).
44. Tomasson, G., Bjornsson, J., Zhang, Y., Gudnason, V. & Merkel, P. A. Cardiovascular risk factors and incident giant cell arteritis: a population-based cohort study. *Scand. J. Rheumatol.* **48**, 213–217 (2019).
45. Wadström, K. et al. Negative associations for fasting blood glucose, cholesterol and triglyceride levels with the development of giant cell arteritis. *Rheumatology* **59**, 3229–3236 (2020).
46. Rhee, R. L., Grayson, P. C., Merkel, P. A. & Tomasson, G. Infections and the risk of incident giant cell arteritis: a population-based, case-control study. *Ann. Rheum. Dis.* **76**, 1031–1035 (2017).
47. Stamatis, P. et al. Infections are associated with increased risk of giant cell arteritis: a population-based case-control study from southern Sweden. *J. Rheumatol.* **48**, 251–257 (2021).
48. Larsson, K., Mellström, D., Nordborg, E., Nordborg, C. & Odén, A. Early menopause, low body mass index, and smoking are independent risk factors for developing giant cell arteritis. *Ann. Rheum. Dis.* **65**, 529–532 (2006).
49. Duhaut, P. et al. Giant cell arteritis and cardiovascular risk factors: a multicenter, prospective case-control study. *Arthritis Rheum.* **41**, 1960–1965 (1998).
50. Bas-Lando, M. et al. The incidence of giant cell arteritis in Jerusalem over a 25-year period: annual and seasonal fluctuations. *Clin. Exp. Rheumatol.* **25**, S15–S17 (2007).
51. Kønig, E. B. et al. Seasonal variation in biopsy-proven giant cell arteritis in eastern Denmark from 1990–2018. *Acta Ophthalmol.* **99**, 527–532 (2021).
52. Gokoffski, K. K., Chatterjee, A. & Khaderi, S. K. Seasonal incidence of biopsy-proven giant cell arteritis: a 20-year retrospective study of the University of California Davis Medical System. *Clin. Exp. Rheumatol.* **37** (Suppl. 117), 90–97 (2019).
53. De Smit, E. et al. Geo-epidemiology of temporal artery biopsy-positive giant cell arteritis in Australia and New Zealand: is there a seasonal influence? *RMD Open* **3**, e000531 (2017).
54. Yates, M., Graham, K., Watts, R. A. & MacGregor, A. J. The prevalence of giant cell arteritis and polymyalgia rheumatica in a UK primary care population. *BMC Musculoskelet. Disord.* **17**, 285 (2016).
55. Smeeth, L., Cook, C. & Hall, A. J. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990–2001. *Ann. Rheum. Dis.* **65**, 1093–1098 (2006).
56. Crowson, C. S. & Matteson, E. L. Contemporary prevalence estimates for giant cell arteritis and polymyalgia rheumatica, 2015. *Semin. Arthritis Rheum.* **47**, 253–256 (2017).
57. Barra, L. et al. Incidence and prevalence of giant cell arteritis in Ontario, Canada. *Rheumatology* **59**, 3250–3258 (2020).
58. Kobayashi, S. et al. Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey. *Arthritis Rheum.* **49**, 594–598 (2003).
59. Mahr, A., Guillevin, L., Poissonnet, M. & Aymé, S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. *Arthritis Rheum.* **51**, 92–99 (2004).
60. Watts, R. A., Lane, S. E., Bentham, G. & Scott, D. G. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum.* **43**, 414–419 (2000).
61. Mohammad, A. J., Jacobsson, L. T. H., Westman, K. W. A., Sturfelt, G. & Segelmark, M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. *Rheumatology* **48**, 1560–1565 (2009).
62. Mohammad, A. J., Jacobsson, L. T. H., Mahr, A. D., Sturfelt, G. & Segelmark, M. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. *Rheumatology* **46**, 1329–1337 (2007).
63. Balcı-Peynircioğlu, B. et al. Comorbidities in familial Mediterranean fever: analysis of 2000 genetically confirmed patients. *Rheumatology* **59**, 1372–1380 (2020).
64. Skochko, S. M. et al. Kawasaki disease outcomes and response to therapy in a multiethnic community: a 10-year experience. *J. Pediatr.* **203**, 408–415.e3 (2018).
65. Yonesaka, S. et al. Biopsy-proven myocardial sequels in Kawasaki disease with giant coronary aneurysms. *Cardiol. Young* **20**, 602–609 (2010).
66. Yonesaka, S. et al. Endomyocardial biopsy in children with Kawasaki disease. *Acta Paediatr. Jpn. Overseas Ed.* **31**, 706–711 (1989).
67. Orenstein, J. M. et al. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study. *PLoS ONE* **7**, e38998 (2012).
68. Numano, F. et al. Galectin-3 is a marker of myocardial and vascular fibrosis in Kawasaki disease patients with giant aneurysms. *Int. J. Cardiol.* **201**, 429–437 (2015).
69. Shibuya, N., Shibuya, K., Kato, H. & Yanagisawa, M. Kawasaki disease before Kawasaki at Tokyo university hospital. *Pediatrics* **110**, e17 (2002).
70. Burns, J. C. History of the worldwide emergence of Kawasaki disease. *Int. J. Rheum. Dis.* **21**, 13–15 (2018).
71. Landing, B. H. & Larson, E. J. Are infantile periarteritis nodosa with coronary artery involvement and fatal mucocutaneous lymph node syndrome the same? Comparison of 20 patients from North America with patients from Hawaii and Japan. *Pediatrics* **59**, 651–662 (1977).
72. Burns, J. C. & Glode, M. P. Kawasaki syndrome. *Lancet* **364**, 533–544 (2004).
73. Kato, H. et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation* **94**, 1379–1385 (1996).
74. Newburger, J. W. et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N. Engl. J. Med.* **315**, 341–347 (1986).
75. Lin, M.-T. & Wu, M.-H. The global epidemiology of Kawasaki disease: review and future perspectives. *Glob. Cardiol. Sci. Pract.* **2017**, e201720 (2017).
76. Ae, R. et al. Epidemiology, treatments, and cardiac complications in patients with Kawasaki disease: the nationwide survey in Japan, 2017-2018. *J. Pediatr.* **225**, 23–29.e2 (2020).
77. Matsubara, Y. et al. Cumulative incidence of Kawasaki disease with cardiac sequelae in Japan. *Pediatr. Int.* **62**, 444–450 (2020).
78. Onouchi, Y. The genetics of Kawasaki disease. *Int. J. Rheum. Dis.* **21**, 26–30 (2018).
79. Huang, Y.-H. et al. Increased incidence of Kawasaki disease in Taiwan in recent years: a 15 years nationwide population-based cohort study. *Front. Pediatr.* **7**, 121 (2019).
80. Kim, G. B. et al. Epidemiology and clinical features of Kawasaki disease in South Korea, 2012–2014. *Pediatr. Infect. Dis. J.* **36**, 482–485 (2017).
81. Jiao, F. et al. The emergence of Kawasaki disease in India and China. *Glob. Cardiol. Sci. Pract.* **2017**, e201721 (2017).
82. Kushner, H. I., Macnee, R. P. & Burns, J. C. Kawasaki disease in India: increasing awareness or increased incidence? *Perspect. Biol. Med.* **52**, 17–29 (2009).
83. Singh, S. et al. Is Kawasaki disease incidence rising in Chandigarh, North India? *Arch. Dis. Child.* **96**, 137–140 (2011).
84. Singh, S. & Bhattad, S. Kawasaki disease incidence at Chandigarh, North India, during 2009–2014. *Rheumatol. Int.* **36**, 1391–1397 (2016).
85. Singh, S., Vignesh, P. & Burgner, D. The epidemiology of Kawasaki disease: a global update. *Arch. Dis. Child.* **100**, 1084–1088 (2015).
86. Manlhiot, C. et al. Epidemiology of Kawasaki disease in Canada 2004 to 2014: comparison of surveillance using administrative data vs periodic medical record review. *Can. J. Cardiol.* **34**, 303–309 (2018).
87. Tulloh, R. M. R. et al. Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. *Arch. Dis. Child.* **104**, 640–646 (2019).
88. Heuclin, T. et al. Increased detection rate of Kawasaki disease using new diagnostic algorithm, including early use of echocardiography. *J. Pediatr.* **155**, 695–699.e1 (2009).
89. Salo, E. et al. Incidence of Kawasaki disease in northern European countries. *Pediatr. Int.* **54**, 770–772 (2012).
90. Maddox, R. A. et al. Kawasaki disease and Kawasaki disease shock syndrome hospitalization rates in the United States, 2006–2018. *Pediatr. Infect. Dis. J.* **40**, 284–288 (2021).
91. Burns, J. C. et al. Seasonality and temporal clustering of Kawasaki syndrome. *Epidemiology* **16**, 220–225 (2005).
92. Burns, J. C. et al. Seasonality of Kawasaki disease: a global perspective. *PLoS ONE* **8**, e74529 (2013).
93. Manlhiot, C. et al. Environmental epidemiology of Kawasaki disease: linking disease etiology, pathogenesis and global distribution. *PLoS ONE* **13**, e0191087 (2018).
94. Rypdal, M. et al. Clustering and climate associations of Kawasaki disease in San Diego County suggest environmental triggers. *Sci. Rep.* **8**, 16140 (2018).
95. Kanegaye, J. T. et al. Lymph-node-first presentation of Kawasaki disease compared with bacterial cervical adenitis and typical Kawasaki disease. *J. Pediatr.* **162**, 1259–1263 (2013).
96. Leuin, S. C. et al. Hoarseness as a presenting sign in children with Kawasaki disease. *Pediatr. Infect. Dis. J.* **32**, 1392–1394 (2013).
97. Gámez-González, L. B. et al. Kawasaki disease presenting with hoarseness: a multinational study of the REKAMLATINA network. *Pediatr. Int.* **63**, 643–648 (2021).
98. Burns, J. C. et al. Temporal clusters of Kawasaki disease cases share distinct phenotypes that suggest response to diverse triggers. *J. Pediatr.* **229**, 48–53.e1 (2021).
99. Hara, T. et al. Assessment of pediatric admissions for Kawasaki disease or infectious disease during the COVID-19 state of emergency in Japan. *JAMA Netw. Open* **4**, e214475 (2021).
100. Shulman, S., Geevarghese, B., Kim, K.-Y. & Rowley, A. The impact of social distancing for COVID-19 upon diagnosis of Kawasaki disease. *J. Pediatr. Infect. Dis. Soc.* **10**, 742–744 (2021).
101. Rodó, X. et al. Revisiting the role of environmental and climate factors on the epidemiology of Kawasaki disease. *Ann. N. Y. Acad. Sci.* **1382**, 84–98 (2016).
102. Jorquera, H., Borzutzky, A., Hoyos-Bachiloglu, R. & Garcia, A. Association of Kawasaki disease with tropospheric winds in central Chile: is wind-borne desert dust a risk factor? *Environ. Int.* **78**, 32–38 (2015).
103. Rodó, X. et al. Tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan. *Proc. Natl Acad. Sci. USA* **111**, 7952–7957 (2014).
104. Makino, N. et al. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015–2016. *Pediatr. Int.* **61**, 397–403 (2019).
105. Nilsen, A. T. et al. Increasing incidence and prevalence of ANCA-associated vasculitis in northern Norway. *Rheumatology* **59**, 2316–2324 (2020).
106. Berti, A., Cornec, D., Crowson, C. S., Specks, U. & Matteson, E. L. The epidemiology of antineutrophil cytoplasmic autoantibody-associated vasculitis in Olmsted County, Minnesota (USA): a 20 year population-based study. *Arthritis Rheumatol.* **69**, 2338–2350 (2017).
107. Andrews, M., Edmunds, M., Campbell, A., Walls, J. & Feehally, J. Systemic vasculitis in the 1980s — is there an increasing incidence of Wegener's granulomatosis and microscopic polyarteritis? *J. R. Coll. Physicians* **24**, 284–288 (1990).
108. Windpessl, M. et al. ANCA status or clinical phenotype — what counts more? *Curr. Rheumatol. Rep.* **23**, 37 (2021).
109. Watts, R. A. et al. Epidemiology of vasculitis in Europe. *Ann. Rheum. Dis.* **60**, 1156–1157 (2001).
110. Pearce, F. A. et al. Incidence of ANCA-associated vasculitis in a UK mixed ethnicity population. *Rheumatology* **55**, 1656–1663 (2016).
111. Pamuk, Ö. N., Dönmez, S., Calayır, G. B. & Pamuk, G. E. The epidemiology of antineutrophil cytoplasmic antibody-associated vasculitis in northwestern Turkey. *Clin. Rheumatol.* **35**, 2063–2071 (2016).
112. Fujimoto, S. et al. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. *Rheumatology* **50**, 1916–1920 (2011).
113. Li, J. et al. The frequency of ANCA-associated vasculitis in a national database of hospitalized patients in China. *Arthritis Res. Ther.* **20**, 226 (2018).
114. Pearce, F. A., Craven, A., Merkel, P. A., Luqmani, R. A. & Watts, R. A. Global ethnic and geographic

differences in the clinical presentations of anti-neutrophil cytoplasm antibody–associated vasculitis. *Rheumatology* **56**, 1962–1969 (2017).
115. Cao, Y. et al. DRB1*15 allele is a risk factor for PR3-ANCA disease in African Americans. *J. Am. Soc. Nephrol.* **22**, 1161–1167 (2011).
116. Pearce, F. A., Grainge, M. J., Lanyon, P. C., Watts, R. A. & Hubbard, R. B. The incidence, prevalence and mortality of granulomatosis with polyangiitis in the UK Clinical Practice Research Datalink. *Rheumatology* **56**, 589–596 (2017).
117. Takala, J. H., Kautiainen, H., Malmberg, H. & Leirisalo-Repo, M. Incidence of Wegener's granulomatosis in Finland 1981–2000. *Clin. Exp. Rheumatol.* **26**, S81–S85 (2008).
118. Sacri, A.-S. et al. Clinical characteristics and outcomes of childhood-onset ANCA-associated vasculitis: a French nationwide study. *Nephrol. Dial. Transpl.* **30** (Suppl. 1), i104–i112 (2015).
119. Mossberg, M., Segelmark, M., Kahn, R., Englund, M. & Mohammad, A. Epidemiology of primary systemic vasculitis in children: a population-based study from southern Sweden. *Scand. J. Rheumatol.* **47**, 295–302 (2018).
120. Gonzalez-Gay, M. A., Garcia-Porrua, C., Guerrero, J., Rodriguez-Ledo, P. & Llorca, J. The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. *Arthritis Rheum.* **49**, 388–393 (2003).
121. Berti, A., Cornec, D., Crowson, C. S., Specks, U. & Matteson, E. L. The epidemiology of antineutrophil cytoplasmic autoantibody-associated vasculitis in Olmsted County, Minnesota (USA): a 20 year population-based study. *Arthritis Rheumatol.* **69**, 2338–2350 (2017).
122. Scott, J., Hartnett, J., Mockler, D. & Little, M. A. Environmental risk factors associated with ANCA associated vasculitis: a systematic mapping review. *Autoimmun. Rev.* **19**, 102660 (2020).
123. Tidman, M., Olander, R., Svalander, C. & Danielsson, D. Patients hospitalized because of small vessel vasculitides with renal involvement in the period 1975-95: organ involvement, anti-neutrophil cytoplasmic antibodies patterns, seasonal attack rates and fluctuation of annual frequencies. *J. Intern. Med.* **244**, 133–141 (1998).
124. Watts, R. A., Mooney, J., Skinner, J., Scott, D. G. I. & Macgregor, A. J. The contrasting epidemiology of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis. *Rheumatology* **51**, 926–931 (2012).
125. Carruthers, D. M., Watts, R. A., Symmons, D. P. M. & Scott, D. G. I. Wegener's granulomatosis — increased incidence or increased recognition? *Br. J. Rheumatol.* **35**, 142–145 (1996).
126. Mahr, A. et al. Seasonal variations in onset of Wegener's granulomatosis: increased in summer? *J. Rheumatol.* **33**, 1615–1622 (2006).
127. Aiyegbusi, O. et al. ANCA-associated renal vasculitis is associated with rurality but not seasonality or deprivation in a complete national cohort study. *RMD Open* **7**, e001555 (2021).
128. Pearce, F. A. et al. Can granulomatosis with polyangiitis be diagnosed earlier in primary care? A case–control study. *QJM . Int. J. Med.* **111**, 39–45 (2018).
129. Gómez-Puerta, J. A., Gedmintas, L. & Costenbader, K. H. The association between silica exposure and development of ANCA-associated vasculitis: systematic review and meta-analysis. *Autoimmun. Rev.* **12**, 1129–1135 (2013).
130. Giorgiutti, S. et al. Prevalence of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and spatial association with quarries in a French northeast region. *Arthritis Rheumatol.* **73**, 2078–2085 (2021).
131. Lane, S. E., Watts, R. A. & Scott, D. G. I. Seasonal variations in onset of Wegener's granulomatosis: Increased in summer? *J. Rheumatol.* **34**, 889–890 (2007).
132. Stamp, L. K. et al. Association between environmental exposures and granulomatosis with polyangiitis in Canterbury, New Zealand. *Arthritis Res. Ther.* **17**, 333 (2015).
133. Gardner-Medwin, J. M. M., Dolezalova, P., Cummins, C. & Southwood, T. R. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet* **360**, 1197–1202 (2002).
134. Kawasaki, Y. et al. The incidence and severity of Henoch-Schönlein purpura nephritis over a 22-year period in Fukushima Prefecture, Japan. *Int. Urol. Nephrol.* **42**, 1023–1029 (2010).
135. Penny, K., Fleming, M., Kazmierczak, D. & Thomas, A. An epidemiological study of Henoch-Schönlein purpura. *Paediatr. Nurs.* **22**, 30–35 (2010).
136. Romero-Gómez, C. et al. Epidemiological study of primary systemic vasculitides among adults in southern Spain and review of the main epidemiological studies. *Clin. Exp. Rheumatol.* **33** (2 Suppl. 89), S11–S18 (2014).
137. Elfving, P. et al. Estimating the incidence of connective tissue diseases and vasculitides in a defined population in northern Savo area in 2010. *Rheumatol. Int.* **36**, 917–924 (2016).
138. Audemard-Verger, A., Pillebout, E., Guillevin, L., Thervet, E. & Terrier, B. IgA vasculitis (Henoch-Shönlein purpura) in adults: diagnostic and therapeutic aspects. *Autoimmun. Rev.* **14**, 579–585 (2015).
139. Sjöwall, C., Mandl, T., Skattum, L., Olsson, M. & Mohammad, A. J. Epidemiology of hypocomplementaemic urticarial vasculitis (anti-C1q vasculitis). *Rheumatology* **57**, 1400–1407 (2018).
140. Lin, Y.-H. et al. Epidemiology of Behcet's disease in Taiwan: a population-based study. *Ophthalmic Epidemiol.* **25**, 323–329 (2018).
141. Lee, Y. B. et al. Incidence, prevalence, and mortality of Adamantiades-Behçet's disease in Korea: a nationwide, population-based study (2006–2015). *J. Eur. Acad. Dermatol. Venereol.* **32**, 999–1003 (2018).
142. Kanecki, K. et al. Behçet disease: a rare systemic vasculitis in Poland. *Pol. Arch. Intern. Med.* **127**, 652–656 (2017).
143. Mohammad, A., Mandl, T., Sturfelt, G. & Segelmark, M. Incidence, prevalence and clinical characteristics of Behcet's disease in southern Sweden. *Rheumatology* **52**, 304–310 (2013).
144. Muruganandam, M. et al. Characteristics of Behcet's disease in the American Southwest. *Semin. Arthritis Rheum.* **49**, 296–302 (2019).
145. Tunes, R. S., Anjos, T. C., Martins, G. B., Barreto, E. R. M. & Santiago, M. B. Prevalence of Behcet's syndrome in patients with recurrent aphthous ulcerations in Brazil. *Rheumatol. Int.* **29**, 875–878 (2009).
146. Fernández-Ávila, D. G., Rincón-Riaño, D. N., Bernal-Macías, S., Dávila, J. M. G. & Rosselli, D. Prevalence and demographic characteristics of Behcet disease in Colombia: data from the national health registry 2012–2016. *Rheumatol. Int.* **40**, 17–20 (2020).
147. Nakae, K. et al. Recent epidemiological features of Behçet's disease in Japan. in *Behçet's Disease* (eds Wechsler, B. & Godeau, P.) 145–151 (Excerpta Medica, 1993).
148. Yurdakul, S. Epidemiology of Behçet syndrome and regional differences in disease expression. in *Behçet's Syndrome* (eds Yazici, Y., Hatemi, G., Seyahi, E. & Yazici, H.) 21–35 (Springer, 2020).
149. Azizlerli, G. et al. Prevalence of Behçet's disease in Istanbul, Turkey. *Int. J. Dermatol.* **42**, 803–806 (2003).
150. Madanat, W. Y. et al. The prevalence of Behçet's disease in the north of Jordan: a hospital-based epidemiological survey. *Clin. Exp. Rheumatol.* **35** (Suppl. 108), 51–54 (2017).
151. Moghimi, N. et al. WHO-ILAR COPCORD study (stage 1, urban study) in Sanandaj, Iran. *Clin. Rheumatol.* **34**, 535–543 (2015).
152. Kim, J. N., Kwak, S. G., Choe, J.-Y. & Kim, S.-K. The prevalence of Behçet's disease in Korea: data from Health Insurance Review and Assessment Service from 2011 to 2015. *Clin. Exp. Rheumatol.* **35** (Suppl. 1), 38–42 (2017).
153. O'Duffy, J. D. Summary of International Symposium on Behçet's Disease. Istanbul, September 29–30, 1977. *J. Rheumatol.* **5**, 229–233 (1978).
154. Li, R. et al. Epidemiology of eight common rheumatic diseases in China: a large-scale cross-sectional survey in Beijing. *Rheumatology* **51**, 721–729 (2012).
155. de Menthon, M., Lavalley, M. P., Maldini, C., Guillevin, L. & Mahr, A. HLA-B51/B5 and the risk of Behçet's disease: a systematic review and meta-analysis of case-control genetic association studies. *Arthritis Rheum.* **61**, 1287–1296 (2009).
156. Ahmad, T. et al. CARD15 polymorphisms in Behçet's disease. *Scand. J. Rheumatol.* **34**, 233–237 (2005).
157. Thomas, T. et al. Epidemiology, morbidity and mortality in Behçet's disease: a cohort study using The Health Improvement Network (THIN). *Rheumatology* **59**, 2785–2795 (2020).
158. Bonitsis, N. G. et al. Gender-specific differences in Adamantiades-Behçet's disease manifestations: an analysis of the German registry and meta-analysis of data from the literature. *Rheumatology* **54**, 121–133 (2015).
159. Yazici, H. et al. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behçet's syndrome. *Ann. Rheum. Dis.* **43**, 783–789 (1984).
160. Yazici, H., Chamberlain, M. A., Tüzün, Y., Yurdakul, S. & Müftüoglu, A. A comparative study of the pathergy reaction among Turkish and British patients with Behçet's disease. *Ann. Rheum. Dis.* **43**, 74–75 (1984).
161. Sibley, C. et al. Behçet syndrome manifestations and activity in the United States versus Turkey — a cross-sectional cohort comparison. *J. Rheumatol.* **41**, 1379–1384 (2014).
162. Kobayashi, T. et al. Differences in clinical manifestations, treatment, and concordance rates with two major sets of criteria for Behçet's syndrome for patients in the US and Japan: data from a large, three-center cohort study. *Mod. Rheumatol.* **23**, 547–553 (2013).
163. Shahram, F. et al. Geographical variations in ocular and extra-ocular manifestations in Behçet's disease. *Eur. J. Rheumatol.* **6**, 199–206 (2019).
164. Kirino, Y. et al. Continuous evolution of clinical phenotype in 578 Japanese patients with Behçet's disease: a retrospective observational study. *Arthritis Res. Ther.* **18**, 217 (2016).
165. Jun, J.-B. et al. Significant decline in the incidence of Behcet's disease in South Korea: a nationwide population-based study (2004–2017). *Arthritis Care Res.* **73**, 1689–1696 (2020).
166. Davatchi, F. et al. Behcet's disease in Iran: analysis of 7641 cases. *Mod. Rheumatol.* **29**, 1023–1030 (2019).
167. Kim, D. Y., Choi, M. J., Cho, S., Kim, D. W. & Bang, D. Changing clinical expression of Behçet disease in Korea during three decades (1983–2012): chronological analysis of 3674 hospital-based patients. *Br. J. Dermatol.* **170**, 458–461 (2014).
168. Hatemi, G. & Yazici, H. Behçet's syndrome and micro-organisms. *Best. Pract. Res. Clin. Rheumatol.* **25**, 389–406 (2011).
169. Mehmood, N., Low, L. & Wallace, G. R. Behçet's disease-do microbiomes and genetics collaborate in pathogenesis? *Front. Immunol.* **12**, 648341 (2021).
170. Park, J. & Cheon, J. H. Incidence and prevalence of inflammatory bowel disease across Asia. *Yonsei Med. J.* **62**, 99–108 (2021).
171. Adeeb, F., Stack, A. G. & Fraser, A. D. New insights into Behçet's disease in Ireland: the Midwest cohort study. *Clin. Exp. Rheumatol.* **36**, 33–39 (2018).
172. Papoutsis, N. G. et al. Prevalence of Adamantiades-Behçet's disease in Germany and the municipality of Berlin: results of a nationwide survey. *Clin. Exp. Rheumatol.* **24**, S125 (2006).
173. Mahr, A. et al. Population-based prevalence study of Behçet's disease: differences by ethnic origin and low variation by age at immigration. *Arthritis Rheum.* **58**, 3951–3959 (2008).
174. Kappen, J. H. et al. Behçet's disease, hospital-based prevalence and manifestations in the Rotterdam area. *Neth. J. Med.* **73**, 471–477 (2015).
175. Villiger, R. A., Stefanski, A.-L., Grobéty, V., Adler, S. & Villiger, P. M. Behçet's syndrome: clinical presentation and prevalence in Switzerland. *Swiss Med. Wkly.* **149**, w20072 (2019).
176. Cartella, S. Prevalence of Behçet's disease in the province of Brescia in northern Italy. *Clin. Exp. Rheumatol.* **32** (4 Suppl. 84), S176 (2014).

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Joint distraction for osteoarthritis: clinical evidence and molecular mechanisms

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Abstract | Joint distraction, the prolonged mechanical separation of the bones at a joint, has emerged as a joint-preserving treatment for end-stage osteoarthritis, with the gradually growing promise of implementation in regular clinical practice. Joint distraction of the knee has been most extensively studied, with these studies showing prolonged symptomatic improvement in combination with repair of cartilage tissue in degenerated knee joints, supporting the concept that cartilage repair can translate into real clinical benefit. The reversal of tissue degeneration observed with joint distraction could be the result of one or a combination of various proposed mechanisms, including partial unloading, synovial fluid pressure oscillation, mechanical and biochemical changes in subchondral bone, adhesion and chondrogenic commitment of joint-derived mesenchymal stem cells or a change in the molecular milieu of the joint. The overall picture that emerges from the combined evidence is relevant for future research and treatment-related improvements of joint distraction and for translation of the insights gained about tissue repair to other joint-preserving techniques. It remains to be elucidated whether optimizing the biomechanical conditions during joint distraction can actually cure osteoarthritis rather than only providing temporary symptomatic relief, but even temporary relief might be relevant for society and patients, as it will delay joint replacement with a prosthesis at an early age and thereby avert revision surgery later in life. Most importantly, improved insights into the underlying mechanisms of joint repair might provide new leads for more targeted treatment options.

With an ageing population and the increasing incidence of obesity, there is a growing demand for joint-preserving treatments for osteoarthritis (OA), a degenerative joint disease characterized by pain and disability owing to joint tissue damage. OA is a huge societal problem, as the disease affects over 10% of the adult population worldwide[1]. Joint preservation is especially relevant in the case of relatively young, middle-aged patients (<65 years old) who are still physically active, as it postpones the need for irreversible surgical treatments such as joint arthroplasty and, as a consequence, averts the requirement for complex, costly revision surgery later in life. Joint-preserving treatment options are increasingly the subject of study, with multiple reviews addressing joint distraction specifically as one of these options[2–4]. Over the past 30 years, joint distraction has emerged as a joint-preserving treatment for patients with end-stage OA who are being considered for joint replacement surgery, with a gradually growing promise for implementation in regular clinical practice. For joint distraction, the two bony ends of a joint are gently separated in a relatively minimally invasive surgery and are held apart at a certain distance for a certain amount of time using an external fixation frame[5]. Joint distraction was first described in the 1990s, for the hip, ankle and foot joints[6–9]. Since then, joint distraction has also been applied to the knee and the base of the thumb[10–12]. A 2013 review of joint distraction studies concluded that the data showed predominantly positive effects of joint distraction, with patients experiencing marked improvements in pain and mobility as well as evidence of cartilage and bone tissue repair activity[2]. Despite this clinical promise, the mechanisms underlying the observed, quite unique, tissue regeneration process in joint distraction were still unknown. Over the intervening years, additional studies have been carried out to identify the molecular mechanisms underlying joint distraction treatment (particularly for the knee) that support the structural changes induced by treatment; this includes research into synovial fluid markers, stem cell involvement and animal studies of tissue repair mechanisms. Furthermore, more extensive clinical trials have been

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Key points

- Joint distraction can induce tissue structure modifications in degenerated knee joints, accompanied by prolonged symptomatic improvement that supports the concept that cartilage repair can translate into real clinical benefit.
- It remains to be elucidated whether achieving optimal biomechanical and molecular conditions during distraction can lead to cure in osteoarthritis rather than providing only temporary symptomatic relief.
- Partial unloading, synovial fluid pressure oscillation, subchondral bone changes, adhesion and chondrogenic commitment of joint-derived mesenchymal stem cells, and an altered molecular milieu in the joint are the proposed mechanisms underlying the therapeutic effects of joint distraction.
- Greater insight into the molecular mechanisms of cartilage repair and their interplay in joint distraction might provide new leads to more targeted treatment options.

performed since 2013, with joint distraction also being applied in regular care for the knee, although still not in large numbers[13].

Compared with other joints, research on knee joint distraction (KJD) has been more extensive, especially with respect to the underlying molecular mechanisms. Therefore, in this Review we focus on KJD and begin by describing the increasing clinical evidence relating to patient-reported symptomatic outcomes as well as repair of cartilage tissue. Next, we discuss the potential molecular mechanisms underlying tissue repair in joint distraction. Finally, we discuss the overall picture emerging from the combined preclinical and clinical evidence, the possible future research and treatment approaches with regard to joint distraction, and translation of mechanistic insights to other joint-preserving techniques.

Clinical evidence

Several clinical trials have been performed in which patients were treated with KJD, in some cases in combination with other treatment modalities. Although the trials differ with regard to the distraction technique and treatment protocol, the general approach remains the same. In all cases, an external frame (FIG. 1) is placed around the knee joint using bone pins on the medial and lateral sides of the femur and tibia, after which the two joint surfaces are held apart at a certain distance for several weeks, followed by removal of the frame and, in general, no follow-up treatment.

Multiple clinical trials of KJD have been completed or are ongoing (TABLE 1; these studies were identified as described in the 'Review criteria'). The first trial of KJD was published in 2007; in this retrospective study six patients with OA were treated with a combination of hinged KJD (using a customized frame) for 2–3 months and bone marrow stimulation[14,15]. Subsequently, in a 2010 case report, a patient with an osteochondral defect was treated with an artificial bone graft and KJD using the same customized hinged frame for 3 months[16]. These studies reported a beneficial effect of KJD in terms of clinical outcome and joint tissue repair, including cartilage repair. In 2011, Intema et al. published the results of the first open prospective study of KJD, in which 20 patients with knee OA were treated for 2 months with joint distraction using the Monotube® Triax™ (Stryker, UK) external fixation system, which completely immobilizes the knee joint[17]. In the same year, a controlled study was published in which 19 patients with OA were treated with a combination of debridement and KJD for 4 weeks using an Ilizarov frame, which also immobilizes the joint during distraction[18]. Both of these studies demonstrated a clear clinical and tissue structure improvement with treatment. Subsequently, two randomized controlled trials (RCTs) comparing 6-week KJD using the Monotube® Triax™ external fixation system with standard treatment (high tibial osteotomy (HTO) in one study and total knee arthroplasty (TKA) in the other) were initiated in 2011 and reported the 1-year follow-up results in 2017. In one of these RCTs, 22 patients with medial compartmental OA indicated for HTO were treated with 6-week KJD and compared with 45 patients treated with HTO[19]. In the other RCT, 20 patients with OA indicated for TKA were treated with 6-week KJD and compared with 36 patients treated with TKA[20]. Both RCTs reported clinical improvement and tissue structure repair with KJD, after 1 year, comparable with changes in HTO and TKA patients. Finally, a retrospective study of 84 patients with OA who were treated with KJD in regular care using the Monotube®

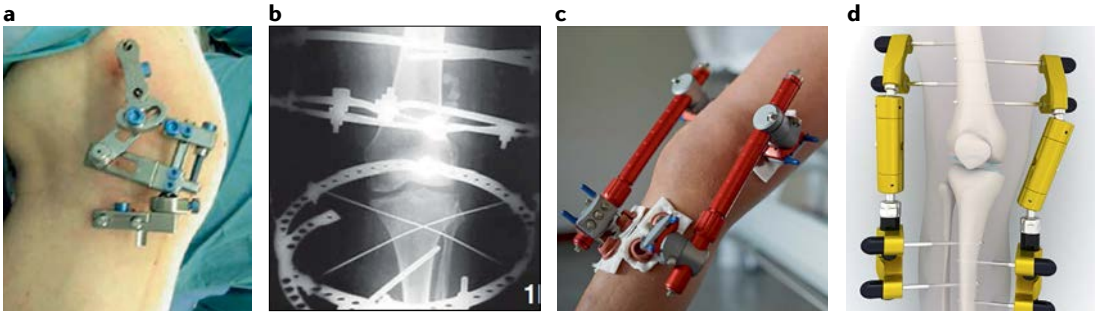

Fig. 1 | **Different type of frames used for knee joint distraction.** Four different frames that have been used in completed or ongoing clinical studies of knee joint distraction are depicted. **a** | A custom articulated distraction device[14]. **b** | The Ilizarov circular frame[18]. **c** | The Monotube® Triax™ external fixation system[27]. **d** | The KneeReviver frame[40,105]. All type of frames rely on comparable mechanical principles and allow movement under loading, leading to synovial pressure changes that are considered essential for stimulating joint repair by joint distraction. Part **a** reprinted with permission from REF.[14], Elsevier. Part **b** republished with the permission of Slack Incorporated, from Aly et al. Arthrodiatasis for management of knee osteoarthritis. *Orthopedics* **34**, e338-43 (2011)[18]; permission conveyed through Copyright Clearance Center, Inc. Part **c** reprinted with permission from REF.[27], SAGE Publications. Part **d**, image courtesy of ArthroSave B. V.

Table 1 | **Clinical studies of knee joint distraction**

Study	Design	Study population	Patient age[a] (years)	Treatment and duration	Follow-up	Outcomes	Refs
Deie et al. (2007) & Deie et al. (2010)	Retrospective	Patients with generalized OA ($n=6$)	51.7 (s.d. 7.8)	Joint distraction (hinged customized device) and BMS; 2–3 months	Mean 2.5 years (range 14–51 months)	PROMs; radiographs; arthroscopy	14,15
Abouheif et al. (2010)	Case report	One patient with an osteochondral defect	18	Joint distraction (hinged customized device) and bone graft; 3 months	4.5 years	Radiographs; arthroscopy; MRI	16
Intema et al. (2011); Wiegant et al. (2013); Van der Woude et al. (2017); Jansen et al. (2018); Jansen et al. (2020)	Prospective	Patients with OA indicated for TKA ($n=20$)	48.5 (SEM 1.3)	Joint distraction (Monotube® Triax™ external fixation system); 2 months	3, 6, 9, 12, 18 and 24 months; 5 years and 9 years	PROMs; radiographs; MRI; systemic biomarkers	17,26–28,35
Aly et al. (2011)	Controlled trial (versus debridement)	Patients with OA ($n=19$)	Range 39–65	Joint distraction (Ilizarov frame) and debridement; 4 weeks	Mean 5.5 years (range 58–82 months)	PROMs; radiographs	18
Van der Woude et al. (2017); Jansen et al. (2019)	RCT (versus HTO)	Patients with OA indicated for HTO ($n=22$)	51.2 (SEM 1.1)	Joint distraction (Monotube® Triax™ external fixation system); 6 weeks	3, 6, 9 and 12 months; 2 years	PROMs; radiographs; MRI; systemic biomarkers	19,29
Van der Woude et al. (2017); Jansen et al. (2019)	RCT (versus total KA)	Patients with OA indicated for total KA ($n=20$)	54.9 (SEM 1.8)	Joint distraction (Monotube® Triax™ external fixation system); 6 weeks	1 and 2 years	PROMs; radiographs; MRI; systemic biomarkers	20,29
Jansen et al. (2020)	Retrospective	Patients with OA ($n=84/41$[b])	53.1 (s.d. 6.9)	Joint distraction (Monotube® Triax™ external fixation system); 6 weeks	1 year	PROMs	13
Ongoing unpublished studies							
Jansen et al.	Prospective	Patients with OA ($n=65$)	Not available	Joint distraction (KneeReviver); 6 weeks	1 year	PROMs; radiographs	21
Pandit et al.	RCT	Patients with OA indicated for partial or total KA ($n=172$)	Not available	Joint distraction (multiple devices); 6 weeks	Recruiting patients	PROMs; radiographs	22

BMS, bone marrow stimulation; HTO, high tibial osteotomy; KA, knee arthroplasty; NA, not applicable; OA, osteoarthritis; PROM, patient-reported outcome measure; RCT, randomized controlled trial; s.d., standard deviation; SEM, standard error of the mean. [a]Average age unless indicated otherwise [b]In cases in which all patients in the trial were or have been evaluated on outcome measures, the number of evaluated patients has been indicated.

Triax™ external fixation system was published in 2020 (REF.[13]). Of these 84 patients, patient-reported outcome measures (PROMs) were available for 41 patients at the 1-year follow-up, and revealed a clear improvement with KJD in regular care.

Most recently, a prospective study was started in late 2017, in which 65 patients with knee OA were treated with 6-week joint distraction using the KneeReviver frame (ArthroSave) and will be followed up for 5 years. A preliminary analysis showed that the first 39 patients reaching the 1-year follow up showed clear improvement in clinical parameters and tissue structure repair, which was generally comparable with and non-inferior to results obtained with 39 patients treated with the Monotube® Triax™ external fixation system in the two RCTs[21]. Last, in the UK, the national multicentre Knee Arthroplasty versus Joint Distraction Study, which is funded by the National Institute for Health Research, started in mid-2021. In the Knee Arthroplasty versus Joint Distraction Study, 344 patients are randomly assigned in a 1:1 ratio to either KJD (using various distraction devices) or knee arthroplasty treatment[22]. All of these studies used different distraction techniques and postoperative rehabilitation protocols (if imposed). Only Deie et al.[14] and Abouheif et al.[16] used hinged distraction, allowing flexion and extension of the knee joint, and continuous passive motion was applied for 2 weeks after placement of the distraction device. All other studies used distraction frames that do not allow joint flexion, although in the study by Intema et al.[17], every 2 weeks the frame was removed and continuous passive motion was applied for 3–4 h, after which the frame was reinstalled and distraction continued. In this study, the clinical effects and tissue structure repair with KJD were slightly better than in the two RCTs[23]. This difference might be related to the use of flexion in Intema et al., although the baseline characteristics of the patient populations and the total duration of joint distraction also differed between these studies. Of note, a customized hinged device was developed for the knee and proved mechanically feasible in a technical feasibility and cadaver study[24]; however, clinical feasibility could not be demonstrated, mainly owing to pain from the motion of soft tissues along the bone pins (S.C.M., unpublished observations

of clinical application of this device in feasibility study). Furthermore, the duration of joint distraction varied from 4 weeks to 3 months in these studies[16,18]. The distraction distance (that is, the separation distance (in millimetres) between the bones) was not clearly described in Deie et al. and Abouheif et al., whereas a distraction of 1 mm/day for 4 weeks was reported in Aly et al. The remaining KJD studies described used a fixed distraction distance of 5 mm. However, it remains unclear how this distance was measured exactly; for example, was the original bone to bone distance or the increase above the original bone to bone distance measured? In addition, correction of the mechanical leg axis was performed during KJD, providing more distance at either side in the case of predominantly unicompartmental knee OA. None of the studies provided a reasoning for their choice of joint distraction distance or duration. For the RCTs, the distraction time was shortened from 2 months to 6 weeks to decrease treatment burden. A post hoc analysis, although insufficiently powered, found that there were no statistically significant differences in primary outcome (all $P > 0.1$) between 6-week and 2-month joint distraction, although patients treated with 2-month KJD showed somewhat better results[23,25]. These KJD studies all evaluated several outcome parameters after treatment (TABLE 1), including patient-reported (clinical) outcomes and outcomes related to cartilage repair, as described further in detail below.

Patient-reported outcomes. All studies evaluated PROMs before and after treatment, except for Abouheif et al., which only mentions that the patient had knee pain before treatment and was pain-free after treatment[16]. In the other studies, pain was self-reported using a visual analogue scale of pain[14], a four-point Likert scale for pain[18], the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale[13,17,19,20,26–29], and/or the Intermittent and Constant Osteoarthritis Pain questionnaire[19,20,29]. For all pain measurements, including at follow-up ranging from 3 months to 9 years (TABLE 1), patients experienced significantly less pain (all $P < 0.05$) after treatment compared with before treatment. Symptom-related PROMs were also evaluated, including walking capacity or stair climbing, the Japanese Osteoarthritis knee score or the WOMAC or Knee Injury and Osteoarthritis Outcome Score (KOOS) and all of their subscales, which evaluate stiffness, function, symptoms, sport and quality of life. In all studies, a statistically significant improvement (all $P < 0.05$) of 40–60% occurred in all of these PROMs at every time point of follow-up (from 1 to 9 years)[13,14,16,18–20,26–30]. Interestingly, even patients who required a TKA several years after KJD treatment still reported increased total WOMAC scores of on average 20 points before undergoing TKA[28]. This increase is higher than the 15-point change considered the minimal clinically important difference and approached statistical significance ($P = 0.067$)[31]. Apparently, other considerations besides symptomatic complaints are important for patients to remain satisfied with their treatment (for example, a relative worsening in symptoms while having TKA as a surgical option). Of note, these studies were retrospective studies, prospective cohort studies, or small RCTs. Thus, their quality is low, especially the retrospective and prospective studies that had no control group, which could be biased, as clinical improvement might be due to the placebo effect. Some of the studies also evaluated quality of life, using the EuroQol-5D and Short Form-36 questionnaires. A statistically significant improvement in EuroQol-5D and in the Short Form-36 physical component summary scores (all $P < 0.05$) but not the mental component summary scores ($P > 0.05$) was observed[19,20,29].

A few of the studies compared KJD with other treatments. For example, Aly et al. compared KJD and debridement ($n = 19$) with debridement alone ($n = 42$). In contrast to patients receiving KJD, those treated with debridement alone did not show a significant improvement (both $P > 0.14$) in pain or walking capacity[18]. In the RCT comparing KJD treatment ($n = 22$) and HTO ($n = 45$), the results of the two groups were generally comparable[19,29], including return to sports and work 5 years after treatment[32]. In the RCT comparing KJD ($n = 20$) and TKA ($n = 36$), no significant differences in outcomes were detected at the 1-year follow up (all $P > 0.05$), but after 2 years almost all PROMs showed considerably greater improvement after TKA than after KJD[20,29]. It is generally accepted that TKA results in substantial improvements in PROMs, although a revision surgery may be needed later in life because of wear and tear and loosening of the prosthesis. The risk of needing revision surgery is much higher in younger patients (<65 years of age), who have a lifetime risk of revision of 15–35%, compared with ~5% on average among older patients (>65 years of age)[33]. Therefore, this population of relatively young and still active patients is specifically indicated for KJD. The average age in all studies fits this consideration (TABLE 1), although data are limited regarding the effects of KJD in the older population. In addition, repeating KJD treatment with several years' interval has never been studied, although anecdotal evidence suggests that a second ankle joint distraction is effective (S.C.M., unpublished observations).

Cartilage tissue restoration. Radiographic measurement of joint space width (JSW) with weight-bearing is the most frequently evaluated parameter for cartilage restoration in clinical studies of KJD, acting as a surrogate measure for change in cartilage thickness. Although Abouheif et al. only mention joint space preservation, qualitatively observed from radiographs, after 4.5 years[16], the other studies quantified JSW changes by measuring the average or minimum JSW[14,17–20,26–29]. All studies found that, on average, JSW increased after KJD treatment, at all measured time points, and almost all increases were statistically significant. The largest increase, from 2.5 mm average JSW before treatment to 4.3 mm at 5.5 years' follow-up, was reported by Aly et al.[18]. The studies that evaluated multiple time points all showed the same general pattern: an initial significant increase in JSW of about 0.5–1.0 mm at the 1-year follow up (all $P < 0.05$), which was sustained over the second year of follow-up[17,19,20,26,29]. A post hoc analysis reported that the increase in minimum JSW at the 1-year

follow-up predicted long-term ability of KJD treatment to postpone TKA[28]. At the 5-year and 7-year follow-ups, the JSW was still above baseline, but the increase was only statistically significant for minimum (both $P<0.05$) but not average JSW of the most affected compartment (both $P>0.3$)[27,28]. Apparently, the advantage of the initial increase in JSW at the 1-year and 2-year follow-ups is maintained, despite the fact that the natural disease progression of OA presumably resumes after treatment.

The use of radiographic JSW measurement does not provide a direct measure of cartilage thickness. For example, partial meniscus extrusion may normalize because of the temporary increase in JSW, enabling the meniscus to reposition and resulting in an increased JSW but not cartilage thickening per se. Actual cartilage tissue repair is supported by MRI or post-treatment arthroscopy evaluation. Deie et al. and Abouheif et al. arthroscopically evaluated the treated knees and showed that hyaline-like cartilage formed after treatment, which Abouheif et al. confirmed by an MRI scan[14,16]. However, most studies did not use arthroscopy so as not to disturb the joint and the ongoing repair processes and because patients were reluctant to interfere with the well-functioning joint. Quantitative MRI evaluation by Intema et al. showed that the average cartilage thickness of the most affected compartment increased significantly ($P<0.001$) from 2.4 mm before treatment to 3.0 mm after treatment[17]. As for the radiographic JSW change at 1-year follow-up, the cartilage thickness change (when corrected for baseline) at the same time point was shown to predict long-term survival of the joint[28]. In addition, the denuded bone area (that is, the percentage of subchondral bone without cartilage) decreased from 22% to 5%[17]. These beneficial changes remained statistically significant at the 2-year follow-up (both $P\leq0.03$) and were still detectable but not statistically significant at the 5-year follow-up (both $P>0.13$)[27]. When patients receiving KJD were compared with matched patients from the OsteoArthritis Initiative who experienced natural disease progression, patients from the OsteoArthritis Initiative showed a significant deterioration in both MRI-measured cartilage thickness and radiographic JSW at 5-year follow-up, whereas patients treated with KJD showed significantly better results (all $P<0.001$)[27]. Even if long-term improvement in cartilage restoration is no longer statistically significant at the 5-year follow-up (all $P>0.1$, except for minimum JSW with $P=0.040$), patients treated with KJD apparently still respond significantly better than if they had instead received conventional treatment in the context of natural OA progression. In the two RCTs, MRI evaluation showed an increase in cartilage thickness and a decrease in the denuded bone area in the most affected compartment at the 2-year follow-up in patients receiving KJD[34]. Long-term results in the prospective study by Intema et al. show that cartilage thickness initially increased from pretreatment levels at the 1-year and 2-year follow-ups but gradually decreased thereafter, although cartilage thickness in both the tibia and femur still exceeded pretreatment levels at the 10-year follow-up[35]. Unfortunately, owing to the cost of repeated scans of patients' knees, the two ongoing KJD studies have not included MRI scans as a primary outcome.

Data are limited with respect to the quality of the cartilage that is regenerated by KJD. The completed prospective study and both RCTs evaluated biomarkers of systemic type II collagen: serum levels of N-terminal propeptide of type IIA procollagen (PIIANP) as a synthesis marker, and urinary levels of C-terminal crosslinked telopeptide of type II collagen (CTX-II) as a degradation marker. In all studies, net type II collagen synthesis (determined by the PIIANP:CTX-II ratio) decreased considerably in the first months after treatment but slowly increased to a marked increase 2 years after treatment[17,26,29]. This result suggests that the regenerated cartilage may be hyaline in nature[36]. For a subgroup of patients in the two RCTs, the change in cartilage quality after KJD treatment was determined using delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), which indicates the glycosaminoglycan (GAG) content of cartilage, and T2 relaxation time data, which reveals the structure of the collagen in cartilage. No significant change was found in dGEMRIC ($P>0.05$), whereas T2 signal values increased after 1 year and subsequently showed a partial normalization at the 2-year follow-up (M.P.J., unpublished observations), even though total knee volume increased, suggesting that cartilage quality did not change[37]. In other words, the newly formed cartilage is likely of a similar quality to that present before treatment and is hyaline cartilage and not fibrocartilage.

In comparison with control treatments, structural outcomes with KJD were generally similar or better. For example, Aly et al. showed that, unlike patients treated with KJD and debridement, those treated with debridement only did not show an increase in JSW[18]. In the two RCTs, there were no significantly different changes in JSW at the 1-year and 2-year follow-ups between the KJD and HTO treatment groups (all $P>0.05$)[19,29]. Because with TKA the entire knee joint is replaced, no comparison of cartilage restoration parameters with KJD or TKA is possible. Furthermore, MRI results from the two RCTs showed that, in contrast to patients treated with KJD, those treated with HTO had increased areas of denuded bone and a significant deterioration in cartilage thickness (both $P<0.05$), and results in patients with severe OA were significantly better for KJD than for HTO (both $P\leq0.02$)[38]. There was no difference between KJD and HTO with regard to dGEMRIC or T2 measurements[37].

Adverse events. The beneficial effects of KJD regarding PROMs and tissue structure repair come at the expense of adverse effects of joint distraction, mostly owing to the placement of external fixation frames. All studies discussed here reported the occurrence of complications except for Abouheif et al.[16]. In all other trials, pin tract skin infections occurred frequently, ranging from 30% (2/6 patients) in the studies by Deie et al.[14,15] to 60% in both RCTs and 85% in the prospective study[17,19,20]. It might be that the skin infection rate is influenced by the positioning and type of pins, with Deie et al. placing the frame more closely to the joint, resulting in less soft-tissue involvement, and using thinner pins (k-wires). Aly et al. report contradictory results regarding skin infection frequency, stating variously that 18% or 74%

of patients experienced skin infections[18]. Regardless, the vast majority (~86%) of all pin tract infections were treatable with oral antibiotics and did not have a significant influence on PROMs at the 1-year follow-up ($P > 0.2$)[13]. Furthermore, despite the high frequency of these infections, patients undergoing TKA surgery years after KJD did not experience any additional complications that could be related to potential latent infection, or decreased clinical benefit[39]. However, superficial skin infections are not trivial, as they are a burden for patients and increase the risk of more serious deeper infections; as such, efforts should be made to decrease the frequency of skin infections. Development of a dedicated frame such as the KneeReviver might be a way to achieve this aim[40]. In addition, care protocols such as the use of cadexomer iodine ointment during distraction treatment, which significantly decreases pin tract infections (from 64% to 32%; $P = 0.010$), might be of use[41].

Complications other than pin tract skin infections occur only sporadically (all <5% among the 172 patients included in the published studies in TABLE 1). The two most frequent adverse events were osteomyelitis (6 patients, 3%) and deep venous thrombosis (4 patients, 2%), which is similar to the frequency of such events in other treatments such as HTO and TKA[29]. Osteomyelitis was treated with pin tract wound cleaning and required administration of a combination of oral and intravenous antibiotics owing to delayed or ineffective treatment of skin infections. Deep venous thrombosis was treated with additional anticoagulation (beyond the preventive anticoagulation that is standard in joint distraction treatment).

Potential mechanisms of joint repair

Despite the fact that joint distraction has been studied for over 20 years, the molecular mechanisms that underlie the observed benefits of this treatment are largely speculative. Published studies relating to this area of research have mostly emerged in the past 5 years[42–44]. To date, several mechanisms have been postulated to be involved in the clinical and structural benefit observed with joint distraction (FIG. 2).

First, joint distraction unloads the joint, temporarily relieving mechanical stress (strain and shear) on the cartilage, which prevents further wear and tear of this tissue. Second, preserved nutrition of the cartilage during mechanical unloading is considered of importance for the health and regeneration of this tissue. Resilience of the distraction frame allows loading and unloading of the joint during distraction, thereby enabling oscillations in joint fluid pressure. Third, transient periarticular osteopenia develops during joint distraction. Mechanical stresses on the bone within the distraction frame are taken over by the frame, which results in permanent diminished subchondral sclerosis and, with that, diminished mechanical impact on the cartilage. Significant changes in bone turnover during and after distraction may provide growth factors, as bone is a store of growth factors that facilitate cartilage repair[45–47]. Moreover, the mechanical and biochemical environment created by joint distraction facilitates cartilage regeneration by stem cells in the different joint tissues, including the synovial tissue and synovial fluid. Last, the altered molecular milieu resulting from mechanical unloading of the joint results in a reset of the balance between anabolism and catabolism in the joint tissue. These proposed mechanisms are discussed in greater detail below.

Mechanical unloading and maintenance of synovial fluid pressure oscillation. OA is influenced in its early and late stages by joint mechanics (loading) and its effects on joint metabolism[48]. The mechanical properties of the joint are severely disturbed in OA, at both the macroscopic and microscopic level. In more advanced disease in particular, overloading of the cartilage and bone is a continuous stimulus for progressive joint degeneration. As such, creating a favourable mechanical environment seems to be a logical prerequisite for enabling repair activity, with unloading of the joint a rational approach to achieving this favourable environment. The reasoning behind the use of mechanical unloading at the joint (using joint distraction and other partial unloading techniques) is clear. The magnitude of the strains on cartilage are important for the fate of cartilage and the chondrocyte response. During normal activities, diurnal strains range from 0 to 10%[49,50], post-activity strains range from 5 to 15%[51–54] and dynamic strains during activity range from 15 to 35%[55,56]. At higher nominal strain magnitudes (50–70%), mechanical compression can cause joint tissue injury[57–59], eventually inducing chondrocyte death via necrosis and apoptosis at the highest strain magnitudes (70–90%)[60,61]. Different loading conditions influence chondrocyte function: static loading decreases cartilage metabolic activity[62], physiological levels of dynamic loading can induce anabolic or anti-inflammatory responses[63–66], whereas hyperphysiological levels of dynamic loading and injurious loading can induce catabolic or pro-inflammatory responses[64,67,68]. Moreover, controlled impact experiments on cartilage tissue indicate that shear stress, rather than impact force, is the strongest predictor of cartilage damage (fissures)[69]. The damaged cartilage in OA might result in a disturbed perception of normal weight-bearing and thereby induce more dedifferentiation of chondrocytes, resulting in further degeneration. These considerations suggest that treatments that temporarily reduce the strain magnitude and shear stress would result in a favourable mechanical environment for allowing repair.

Joint distraction reduces loading of cartilage and bone, although this mechanical unloading is most likely only partial. During treatment, patients are encouraged to walk and place a load on their distracted joint. In most instances, there will most likely be contact between the articular surfaces during loading of the joint owing to resilience in the distraction frames (M.P.J. and S.C.M., unpublished observations from the mechanical bench testing of different devices). This observation is supported by a previous study demonstrating that there is contact between the joint surfaces of cadaveric ankles undergoing 5-mm distraction under 70-kg loading[70]. Irrespective of the extent of unloading, a condition is created in which mechanical overload (strain and shear), an important driving force of joint degeneration, is temporally neutralized. Moreover, in the case of non-articulating devices, shear stresses are completely

Stress
Subject to pressure or tension.

Strain
Relative deformation or change in shape and size of elastic, plastic and fluid materials under applied forces.

Shear
A force tending to cause deformation of a material by slippage along a plane or planes parallel to the imposed stress.

absent. This absence of mechanical wear and tear on the cartilage is considered to be of importance to allow joint repair. Chondrocytes are sensitive to mechanical stimuli to maintain cartilage integrity[71], which means that complete immobilization and the absence of any mechanical stimulation of chondrocytes might be counterproductive. At present, it is unknown to what degree (that is, the magnitude and frequency of) mechanical

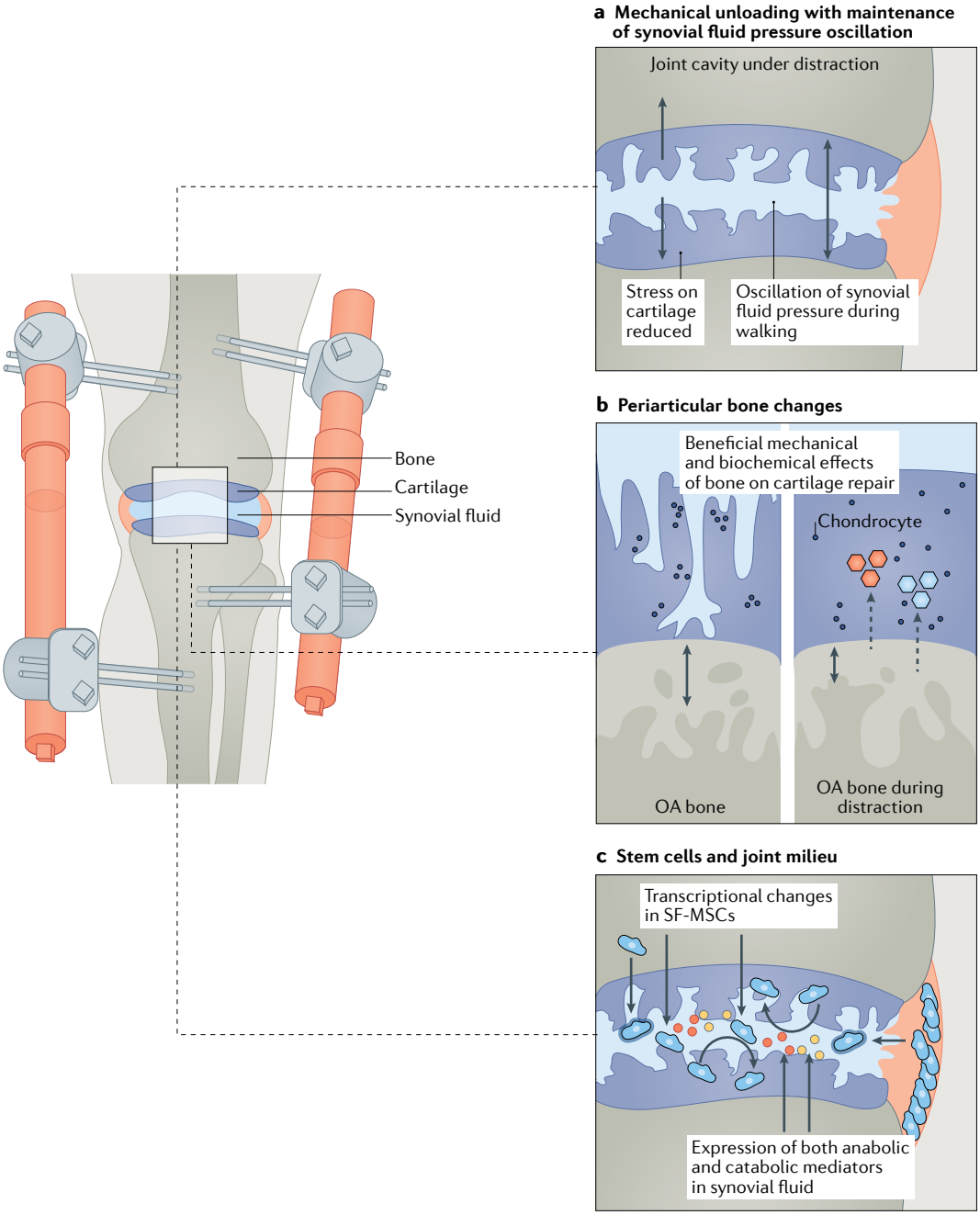

Fig. 2 | **Overview of joint processes and molecular mechanisms during and after joint distraction.** Distraction changes the osteoarthritis (OA)-related homeostasis in the joint. **a** | Joint distraction reduces mechanical (over)load on the articular cartilage surfaces, thereby preventing wear and tear and potentially initiating intrinsic cartilage repair activity. Resilience in the distraction frame causes synovial fluid pressure changes during loading and unloading of the joint, improving the nutrition of the cartilage and stimulating the repair activities and processes of chondrocytes. **b** | Joint distraction also results in considerable peri-articular bone changes. Altered activity of bone cells may add to release of trophic factors (hexagonal shapes) to support cartilage repair. **c** | Restoration of the mechanical and biochemical environment of the joint, including the loss of the hyaluronic acid coating (blue outline) from synovial fluid-derived mesenchymal stem cells (SF-MSCs), might therefore provide a window of opportunity in which joint-resident MSCs can attach to injury sites and repair tissues. Adapted from REF.[2], Springer Nature Limited. Schematic of distracted knee joint (left) adapted with permission from BMJ Publishing Group Limited: Intema, F. et al. Tissue structure modification in knee osteoarthritis by use of joint distraction: an open 1-year pilot study. *Ann. Rheum. Dis.* **70**, 1441–1446 (2011)[17].

contact between cartilage surfaces during loading of the distracted joint is a prerequisite for facilitating cartilage tissue repair. How repair is related to deviation from an optimal unloading level is unknown. The exact force and frequency of mechanical loading will be highly variable between patients in daily practice and might explain the variability in joint tissue repair activity observed in clinical studies. Future studies that take mechanical loading into account, by recording and controlling resilience in the distraction device, managing the body weight of patients and determining the actual loading of the joint during distraction, are warranted to understand the influence of this parameter on joint repair and potentially improve repair activity if an optimal unloading can be achieved for each patient.

Of note, variation in resilience in joint distraction devices creates a condition that is different from complete immobilization, such as that obtained by casting. As mentioned previously, loading of the affected joint is encouraged during joint distraction, resulting not only in partial mechanical contact between the cartilage surfaces but also in joint fluid pressure oscillations because of the stiffness of the joint capsule when the two bone ends approach each other during loading. The combination of loading and resilience of the distraction frame and the stiffness of the joint capsule provides fluctuation of the intra-articular fluid pressure, as occurs naturally during normal loading and unloading of a joint[7]. Not only is this intermittent fluid pressure oscillation considered essential for nourishment of the cartilage but it also plays a role as a mechanical stimulus for the chondrocytes in the anisotropic cartilage extracellular matrix. In vitro studies have demonstrated that these fluid pressure changes are beneficial specifically to OA cartilage[72], whereas normal healthy cartilage seems less sensitive to these fluid pressure changes. Moreover, these fluid pressure changes result in diminished inflammatory activity of OA synovial cells[73], with reduced production of catabolic cytokines such as IL-1 and tumour necrosis factor (TNF). Other joint-saving techniques with partial unloading, such as tibial osteotomy or unicompartmental load-absorbing implants (that is, the Atlas system), show clinical improvements[74] and even beneficial structural changes[75–77]. Both techniques considerably reduce medial compartment contact pressure and peak contact pressure[78,79] and also maintain joint fluid pressure oscillations. Clearly, more research is needed to determine the most favourable hydromechanical and mechanical conditions during (and after) distraction treatment.

Periarticular bone changes. The substantial bone changes that occur during joint distraction, a process that starts with inducing osteopenia followed by normalization of bone characteristics after treatment, are considered to constitute another important promoter of cartilage repair. Moreover, bone changes may be a key factor in the pain relief observed with joint distraction. The mechanical stresses during joint distraction are borne by the distraction frame, which is connected to the bone pins and fixed at both bone ends. This reduction of direct stresses on the bone will result in osteopenia during joint distraction, even during loading and unloading of the joint during distraction, because the bone within the outer bone pins will remain partially mechanically unloaded[80]. A study in which patients with advanced post-traumatic OA were treated with ankle distraction found an overall decrease in subchondral bone density, which persisted until at least the 2-year follow-up[30,81]. Before treatment, the subchondral bone had regions of relatively low density (cystic areas) and relatively high density (sclerotic areas). Although overall density decreased after treatment, density in cystic lesions increased, indicating an overall normalization of bone density.

A similar decrease and normalization in bone density has been reported with KJD[17]. The disappearance of cystic areas might be mechanistically related to the changes in the mechanical and biochemical environment induced by joint distraction. Cysts represent regions of bone necrosis[82] and have the potential to not only increase but also diminish[83] over time. Decreased sclerosis in the area surrounding cystic lesions and, subsequently, less stiff bone, may allow mechanical stimuli to reach the cystic area and induce bone formation. This combination of regional bone loss and growth with an overall increase in bone turnover might be necessary for repair of cystic areas. To date, no clear associations have been found between clinical improvement and overall bone changes. However, a strong correlation has been found between the resolution of cysts and clinical improvement in the case of ankle distraction, as determined by patient-reported outcome[30]. Cyst-related joint pain might be caused by increased pressure and fluid flow in the subchondral bone. During loading, compression of cartilage forces fluid into the bone through the damaged subchondral plate[84]. The hydraulic conductance of osteochondral tissue is higher in patients with OA than in healthy individuals[85]. When cysts and defects in the subchondral plate diminish, the subchondral bone is less subject to increased fluid flow and pressure, resulting in decreased joint pain. Cystic pores within the cortical plate close to the joint surface result in an increase in hydraulic conductance, which might be responsible for joint pain. Bone cysts, as well as bone surface attrition, seem to evolve in regions of bone marrow lesions and are suggested to be the next stage of bone marrow pathology[86]. The correlation between bone marrow lesions observed by MRI and clinical symptoms is well-established and could also be explained by increased pressure within the bone in areas of excessive loading and mechanically compromised trabecular structure[86,87], thereby providing a rational explanation for the decreased pain as a result of KJD.

In addition to the mechanical effects of joint distraction, the substantial changes in bone turnover resulting from osteopenia and subsequent bone density normalization most likely result in the release of growth factors from the large store of these molecules in the bone. These mechanical and biochemical interactions might not only be involved in the clinical and structural benefits of KJD (and joint distraction in general) but might also explain the tissue repair observed with osteotomy, an intervention that is also accompanied by substantial bone turnover. As the exact growth factors are not yet identified in the context of KJD (and HTO), we might learn a lot from

advances in the understanding of distraction histogenesis, a distraction technique that is successfully applied to overcome difficult orthopaedic conditions such as limb deformities, non-unions and segmental bone defects. Although applied differently, distraction triggers both local and systemic responses that contribute to bone regeneration, including the production of bone morphogenetic proteins[88] and inflammatory factors[89], as well as mechanotransduction signals (such as the Hippo and Wnt signalling pathways)[90], among others.

Moreover, a study in a canine model of OA further supports the involvement of bone changes in the cartilage repair process induced by KJD[91]. In this study, aimed at demonstrating the beneficial structural effects of KJD, animals were assigned to no treatment, KJD treatment and an additional treatment, 'frame non-distraction', involving fitting an external fixed frame without distraction. Remarkably, this additional treatment produced clear bone turnover changes and had a moderate beneficial effect on cartilage (improved histology and cartilage proteoglycan turnover) compared with no treatment, although the effects were inferior to those with KJD. The structural improvement with this frame non-distraction treatment might be due to the partial unloading with maintained joint mobility. Owing to their quadrupedalism, animals receiving frame non-distraction treatment loaded their treated joints less than those animals receiving no treatment. These data suggest that a combination of hydromechanical and mechanical changes in cartilage and bone turnover changes are likely needed to obtain the observed effects of distraction.

Stem cells and the joint milieu. An impressive outcome of KJD is the considerable reduction of denuded bone areas observed by MRI, where these areas are filled in with tissue with a signal intensity similar to that of the original cartilage[17,34]. It seems unlikely that this effect is due solely to increased extracellular matrix synthesis by chondrocytes surrounding the gaps. It is postulated that resident mesenchymal stem cells (MSCs) in the joint[92–94] are important for the intra-articular repair activity. The presence of MSCs in the different joint tissues, such as synovium, cartilage and synovial fluid, supports this hypothesis[92]. The exact contribution of MSCs is unclear but they might stimulate the metabolism of pre-existing chondrocytes or themselves differentiate into chondrocytes. Nonetheless, the first studies of MSCs and mediators released in the context of distraction have emerged recently.

In vitro, OA synovial fluid and purified high molecular weight hyaluronic acid inhibit adhesion of synovial fluid-derived MSCs (SF-MSCs)[42]. Treatment of OA synovial fluid with hyaluronidase increases this attachment fourfold, indicating that in OA the MSCs are coated with a layer of hyaluronic acid that prevents these cells from attaching to the injury site. Moreover, in a canine KJD model, MSCs are able to attach to the damaged cartilage in the distracted joint, and this is dependent on the molecular weight of the hyaluronic acid. Thus, distraction seems to rescue the ability of SF-MSCs to adhere to damaged tissue, an ability that is considered key for MSC-mediated colonization, differentiation and repair of cartilage.

Although the exact mechanisms involved are largely unknown, endogenous subchondral bone MSCs (SB-MSCs) and SF-MSCs have been suggested as potential contributors to structural improvement and cartilage repair after unloading[68,95,96]. Gene expression analysis of MSCs isolated from synovial fluid of patients with OA showed that SF-MSCs express lower levels of the ossification- and hypotrophy-related genes parathyroid hormone 1 receptor and runt-related transcription factor, respectively, than SB-MSCs[43]. This result might indicate the greater cartilage remodelling ability of OA SF-MSCs than SB-MSCs. Interestingly, joint unloading by KJD results in a sustained and significant increase in the size and density of SF-MSC colonies. In addition, expression of the key cartilage core protein aggrecan increased and that of the pro-inflammatory chemokine CCL2 (also known as MCP1) decreased during joint distraction[43]. The first 3 weeks of joint distraction treatment were marked by distinct increases in MSC chondrogenic commitment markers such as gremlin 1 and growth differentiation factor 5 (GDF5), which are associated with healthy cartilage homeostasis[97–100]. These results indicate that the transcriptome of joint-resident MSCs differs depending on the biomechanical environment (that is, fluid or bone) and that temporary unloading leads to transcriptional changes in SF-MSCs that might be important in cartilage repair.

In addition to changes in MSCs, KJD also induces molecular changes in synovial fluid. In a study of 20 patients with OA treated with KJD, synovial fluid was sampled at the baseline, midpoint (3 weeks) and end point (6 weeks) of joint distraction and ten predefined mechanosensitive molecules were measured[44]. Statistically significant changes were detected between the pretreatment and end-point samples for 6 of 10 markers: activin A levels decreased to within normal range for most individuals, whereas the levels of transforming growth factor-β (TGFβ), monocyte chemoattractant protein 1 (MCP1), IL-6, fibroblast growth factor 2 (FGF2) and latent-transforming growth factor-beta-binding protein 2 (LTBP2) increased in most patients. For most analytes, changes were detectable at the midpoint of distraction treatment (3 weeks), although the response for some analytes, such as LTBP2, was variable. The levels of the remaining four markers, IL-8, matrix metalloproteinase 3 (MMP3), tissue inhibitor of metalloproteinases 1 (TIMP1) and TNF-inducible gene 6 protein (TSG6; also known as TNFAIP6) at 6 weeks did not differ significantly from pretreatment levels, although IL-8 and TIMP1 levels at the midpoint were significantly higher than before treatment ($P < 0.01$ and $P < 0.05$, respectively). Although this study lacked the power to fully test for an association between marker changes and clinical outcome, some tentative associations between changes in marker levels and subsequent changes in KOOS at the 12-month follow-up were observed. Patients achieving the minimum clinically important difference in KOOS of 10 points at the 6-month follow-up had greater increases in FGF2 and TGFβ levels than those who did not. An increase in IL-8 level during the 6-week treatment period was associated with a significantly greater improvement in KOOS at the 12-month follow up ($P < 0.04$).

Moreover, the increased FGF2 and TGFβ levels might be related to the enhanced expression of TGFβ receptor type 1 (TGFBR1) and TGFBR2 that is observed in SF-MSCs early during KJD treatment[43], which might signify an enrichment in TGFβ-responsive MSCs during these early treatment stages. As seen in the SF-MSC gene expression study[43], detectable, meaningful molecular changes that are observed in synovial fluid after joint distraction are providing additional clues about the mechanisms underlying the clinical and structural changes induced by this treatment. Despite these insights, some observations are puzzling, especially regarding the levels of some pro-inflammatory mediators in synovial fluid. For example, CCL2 expression by SF-MSCs was lower after joint distraction[43], whereas IL-6 and CCL2 levels in synovial fluid were higher after KJD[44]. CCL2 is increased in synovial fluid of patients with OA and associated with chondrocyte degeneration and synovial inflammation and is implicated in joint pain[101,102]. These observations also contrast with results from animal studies in which KJD led to an decrease in joint inflammation[91,95]. An interesting hypothesis is that mechanical unloading induces both catabolic and reparative responses at the moment when the joint surfaces are distracted, but additional time is needed to fully shift to a reparative state. This hypothesis is supported by the change in the PIIANP:CTX-II ratio (indicating type II collagen turnover) in patients treated with KJD, which indicates a shift from breakdown towards synthesis between the 6-month and the 12-month follow-up[26,29]. This result is in line with recent preliminary research demonstrating that such a catabolic to an anabolic shift in the joint occurs within 10 weeks after joint distraction in a canine model of KJD, as indicated by type II collagen marker levels, cartilage proteoglycan turnover and a catabolic transcription profile of cartilage tissue[103]. This result hints that not only during distraction, where processes are initiated, but also the post-distraction period seems to be essential to reach a reparative state. To further expand and evaluate the effects found thus far, larger studies are clearly needed, both clinical and preclinical, with multiple time points, both during and after treatment and focusing on broader sets of markers and transcripts.

Box 1 | **Future directions in knee joint distraction research and treatment**

Improving individual patient response

- Better patient selection before treatment
- Personalized treatment approach

Implementation in regular clinical care

- Establishing consensus guidelines for treatment
- Arranging treatment reimbursement

Further understanding of molecular mechanisms underlying joint repair

- Use of novel imaging techniques in combination with established and novel biomarkers
- Evaluating additional local or systemic tissue repair and inflammation biomarkers
- Evaluating the role of other factors (for example, microRNA, gait and mesenchymal stem cell origin) in joint repair

Translating knowledge from KJD studies beyond joint distraction

- Applying insights from different components of knee joint distraction (KJD) treatment and the resulting joint repair processes to other OA treatments

Future directions

KJD improves clinical results and promotes tissue restoration, and knowledge about the underlying molecular mechanisms is increasing, although several steps could and should be taken in the future to further advance KJD research and treatment (BOX 1). Although at the population level patients treated with KJD show long-lasting clinical improvement, it is important to realize that not all patients respond well to this treatment. KJD treatment response is better in male than in female patients and in patients with more severely affected joints, but variability in the response to treatment might also be related to processes or characteristics that have not yet been identified or investigated. Improving patient selection before treatment is crucial to increase the likelihood that patients will respond well to treatment. In addition, a more personalized treatment approach or combining joint distraction with other remedies should be considered. Furthermore, wider implementation of joint distraction in regular clinical care is required. To date, KJD has been applied almost exclusively under trial conditions and has been used in regular clinical care in only a limited number of hospitals in The Netherlands. Internationally, both patients and surgeons are interested in KJD, but widespread clinical implementation of a new treatment is a slow and challenging process. Some steps have been made towards this goal, such as the development of a dedicated device for KJD treatment (the KneeReviver), but necessary future steps include establishing consensus guidelines for treatment and rehabilitation and arranging treatment reimbursement.

Despite these encouraging developments in recent years, a better understanding of tissue repair mechanisms in joint distraction is warranted. Our knowledge could be improved with the greater use of novel imaging techniques, such as 7-T MRI using advanced protocols (for example, glycosaminoglycan chemical exchange saturation transfer imaging (GagCEST) or sodium MRI), ideally in combination with synovial fluid marker evaluation. These measures could also improve patient selection. Furthermore, the use of other local or systemic markers of tissue repair and inflammation should be considered and novel markers should be identified. For example, the role of miRNAs and extracellular vesicles in relation to senescence in OA is recognized[104]. It might well be that KJD also influences these processes of senescence and that they are part of the mechanism of tissue repair. Moreover, the role of unloading should be studied further, by implementing tools such as advanced gait analysis before, during and after treatment and computational modelling of gait and joint repair. In addition, the involvement of MSCs in joint repair requires further study. Although initial studies have focused on the involvement of MSCs derived from synovial fluid, these cells might originate from the synovial tissue. Cartilage-resident progenitors could also be involved in joint repair and might become activated during joint distraction, and senescent and/or dying chondrocytes could also be cleared during joint distraction. Importantly, the

different components of KJD treatment and the joint processes that are induced by joint distraction could be translated into other treatments for OA that thus far have not shown the desired efficacy.

Conclusions

Evidence is gradually accumulating that KJD results in prolonged pain relief in patients with OA and that it can reverse the tissue degeneration process in OA. It remains to be elucidated whether optimizing the biomechanical conditions during distraction can actually lead to cure of OA rather than only providing temporary symptomatic relief. Even if relief is only temporary, KJD might still be of relevance to patients and society, as this treatment has shown the potential to delay the need for a prosthesis at an early age and thereby prevent the requirement for revision surgery later in life. Most importantly, better insight into the underlying mechanisms of cartilage repair in joint distraction might provide new leads to more targeted treatment options. For example, MSC enrichment in the correct joint milieu might alone provide sufficient repair activity without the need for distraction treatment (and its associated burden, including temporary physical limitations, discomfort and pain), although presumably the mechanical conditions during joint distraction (temporary absence of wear and tear and bone turnover) might also be essential for the repair process.

Providing the correct joint milieu, both mechanically and biochemically, has the potential to stimulate joint repair. The difference with the many trial-and-error treatment attempts to date is that we can learn from distraction and just need to unravel the mechanisms that lead to this repair.

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1. Hunter, D. J. & Bierma-Zeinstra, S. Osteoarthritis. *Lancet* **393**, 1745–1759 (2019).
2. Mastbergen, S. C., Saris, D. B. F. & Lafeber, F. P. J. G. Functional articular cartilage repair: Here, near, or is the best approach not yet clear? *Nat. Rev. Rheumatol.* **9**, 277–290 (2013).
3. Palmer, J. S. et al. Surgical interventions for symptomatic mild to moderate knee osteoarthritis. *Cochrane Database Syst. Rev.* **7**, CD012128 (2019).
4. Jatinder Singh, L., Salim AL, H. & Suwailim AL, G. Surgical options for treating knee osteoarthritis — a concise review. *J. Musculoskelet. Disord. Treat.* **6**, 084 (2020).
5. Lafeber, F. P., Intema, F., Van Roermund, P. M. & Marijnissen, A. C. Unloading joints to treat osteoarthritis, including joint distraction. *Curr. Opin. Rheumatol.* **18**, 519–525 (2006).
6. Aldegheri, R., Trivella, G. & Saleh, M. Articulated distraction of the hip: conservative surgery for arthritis in young patients. *Clin. Orthop. Relat. Res.* **301**, 94–101 (1994).
7. Van Valburg, A. A. et al. Can Ilizarov joint distraction delay the need for an arthrodesis of the ankle? A preliminary report. *J. Bone Jt. Surg. B* **77**, 720–725 (1995).
8. Van Valburg, A. A. et al. Joint distraction in treatment of osteoarthritis: a two-year follow-up of the ankle. *Osteoarthritis Cartilage* **7**, 474–479 (1999).
9. Bain, G. I., Mehta, J. A., Heptinstall, R. J. & Bria, M. Dynamic external fixation for injuries of the proximal interphalangeal joint. *J. Bone Jt. Surg. B* **80**, 1014–1019 (1998).
10. DeVries, J. G., Amiot, R. A., Cummings, P. & Sockrider, N. Freiberg's infraction of the second metatarsal treated with autologous osteochondral transplantation and external fixation. *J. Foot Ankle Surg.* **47**, 565–570 (2008).
11. Spaans, A. J., van Minnen, L. P., Braakenburg, A. & Mink van der Molen, A. B. Joint distraction for thumb carpometacarpal osteoarthritis: a feasibility study with 1-year follow-up. *J. Plast. Surg. Hand Surg.* **51**, 254–258 (2017).
12. Jansen, M. P. et al. Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit: a systematic review and meta-analysis of the limited number of studies and patients available. *Cartilage* https://doi.org/10.1177/1947603520942945 (2020).
13. Jansen, M. P. et al. Knee joint distraction in regular care for treatment of knee osteoarthritis: a comparison with clinical trial data. *PLoS ONE* **15**, e0227975 (2020).
14. Deie, M., Ochi, M., Adachi, N., Kajiwara, R. & Kanaya, A. A new articulated distraction arthroplasty device for treatment of the osteoarthritic knee joint: a preliminary report. *Arthroscopy* **23**, 833–838 (2007).
15. Deie, M. et al. Knee articulated distraction arthroplasty for the middle-aged osteoarthritic knee joint. *Tech. Knee Surg.* **9**, 80–84 (2010).
16. Abouheif, M. M. et al. Repair of a large osteochondral defect in the knee joint using autologous and artificial bone graft combined with motion preserving distraction arthroplasty: a case report. *Arch. Orthop. Trauma. Surg.* **130**, 231–236 (2010).
17. Intema, F. et al. Tissue structure modification in knee osteoarthritis by use of joint distraction: an open 1-year pilot study. *Ann. Rheum. Dis.* **70**, 1441–1446 (2011).
18. Aly, T. A., Hafez, K. & Amin, O. Arthrodiatasis for management of knee osteoarthritis. *Orthopedics* **34**, e338–e343 (2011).
19. van der Woude, J. A. D. et al. Knee joint distraction compared with high tibial osteotomy: a randomized controlled trial. *Knee Surg. Sport. Traumatol. Arthrosc.* **25**, 876–886 (2017).
20. Van Der Woude, J. A. D. et al. Knee joint distraction compared with total knee arthroplasty a randomised controlled trial. *Bone Jt. J.* **99-B**, 51–58 (2017).
21. Jansen, M. P. Knee joint distraction: moving forward. (Utrecht University, 2021).
22. ISRCTN. A comparison of knee replacement surgery and knee joint distraction for treating osteoarthritis of the knee (2020).
23. van der Woude, J. A. D. et al. Six weeks of continuous joint distraction appears sufficient for clinical benefit and cartilaginous tissue repair in the treatment of knee osteoarthritis. *Knee* **23**, 785–791 (2016).
24. Struik, T. et al. Technical feasibility of personalized articulating knee joint distraction for treatment of tibiofemoral osteoarthritis. *Clin. Biomech.* **49**, 40–47 (2017).
25. Wiegant, K. et al. Knee joint distraction as an alternative surgical treatment for osteoarthritis: rationale and design of two randomized controlled trials (vs high tibial osteotomy and total knee prosthesis). *Int. J. Orthop.* **2**, 353–360 (2015).
26. Wiegant, K. et al. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. *Osteoarthritis Cartilage* **21**, 1660–1667 (2013).
27. van der Woude, J. T. A. D. et al. Five-year follow-up of knee joint distraction: clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. *Cartilage* **8**, 263–271 (2017).
28. Jansen, M. P. et al. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. *Osteoarthritis Cartilage* **26**, 1604–1608 (2018).
29. Jansen, M. P. et al. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. *Cartilage* **12**, 181–191 (2019).
30. Intema, F. et al. Subchondral bone remodeling is related to clinical improvement after joint distraction in the treatment of ankle osteoarthritis. *Osteoarthritis Cartilage* **19**, 668–675 (2011).
31. Escobar, A. et al. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. *Osteoarthritis Cartilage* **15**, 273–280 (2007).
32. Hoorntje, A. et al. Return to sport and work after randomization for knee distraction versus high tibial osteotomy: is there a difference? *J. Knee Surg.* https://doi.org/10.1055/s-0040-1721027 (2020).
33. Bayliss, L. E. et al. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. *Lancet* **389**, 1424–1430 (2017).
34. Jansen, M. P. et al. Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy — post-hoc analyses of two randomized controlled trials. *J. Clin. Med.* **10**, 368 (2021).
35. Jansen, M. P., Mastbergen, S. C., MacKay, J. W., Turmezei, T. D. & Lafeber, F. Knee joint distraction results in MRI cartilage thickness increase up to ten years after treatment. *Rheumatology* https://doi.org/10.1093/rheumatology/keab456 (2021).
36. van Spil, W. E., DeGroot, J., Lems, W. F., Oostveen, J. C. M. & Lafeber, F. P. J. G. Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. *Osteoarthrits Cartilage* **18**, 605–612 (2010).
37. Besselink, N. J. et al. Cartilage quality (dGEMRIC Index) following knee joint distraction or high tibial osteotomy. *Cartilage* **11**, 19–31 (2018).
38. Jansen, M. P. et al. Knee joint distraction is more efficient in rebuilding cartilage thickness in the more affected compartment than high tibial osteotomy in patients with knee osteoarthritis. *Osteoarthritis Cartilage* **27**, S330–S331 (2019).
39. Wiegant, K. et al. Total knee prosthesis after knee joint distraction treatment. *J. Surg. Surg. Res.* **1**, 066–071 (2015).
40. Jansen, M. P., Struijk, T., Mastbergen, S. C., Custers, R. J. & Lafeber, F. P. User-friendliness of a novel dedicated knee joint distraction device: experiences from clinical practice. *Osteoarthritis Cartilage* **28**, S474 (2020).
41. Jansen, M. P. et al. Reduction of pin tract infections during external fixation using cadexomer iodine. *J. Exp. Orthop.* **7**, 88 (2020).
42. Baboolal, T. G. et al. Synovial fluid hyaluronan mediates MSC attachment to cartilage, a potential novel mechanism contributing to cartilage repair in osteoarthritis using knee joint distraction. *Ann. Rheum. Dis.* **75**, 908–915 (2016).
43. Sanjurjo-Rodriguez, C. et al. Gene expression signatures of synovial fluid multipotent stromal cells in advanced knee osteoarthritis and following knee joint distraction. *Front. Bioeng. Biotechnol.* **8**, 1178 (2020).
44. Watt, F. E. et al. The molecular profile of synovial fluid changes upon joint distraction and is associated with clinical response in knee osteoarthritis. *Osteoarthritis Cartilage* **28**, 324–333 (2020).
45. Caldwell, K. L. & Wang, J. Cell-based articular cartilage repair: the link between development and regeneration. *Osteoarthritis Cartilage* **23**, 351–362 (2015).
46. Funck-Brentano, T. & Cohen-Solal, M. Crosstalk between cartilage and bone: when bone cytokines matter. *Cytokine Growth Factor. Rev.* **22**, 91–97 (2011).
47. Yuan, X. L. et al. Bone-cartilage interface crosstalk in osteoarthritis: potential pathways and future therapeutic strategies. *Osteoarthritis Cartilage* **22**, 1077–1089 (2014).

48. Griffin, T. M. & Guilak, F. The role of mechanical loading in the onset and progression of osteoarthritis. *Exerc. Sport. Sci. Rev.* **33**, 195–200 (2005).
49. Widmyer, M. R. et al. High body mass index is associated with increased diurnal strains in the articular cartilage of the knee. *Arthritis Rheum.* **65**, 2615–2622 (2013).
50. Coleman, J. L. et al. Diurnal variations in articular cartilage thickness and strain in the human knee. *J. Biomech.* **46**, 541–547 (2013).
51. Eckstein, F. et al. Effect of physical exercise on cartilage volume and thickness in vivo: MR imaging study. *Radiology* **207**, 243–248 (1998).
52. Eckstein, F., Hudelmaier, M. & Putz, R. The effects of exercise on human articular cartilage. *J. Anat.* **208**, 491–512 (2006).
53. Eckstein, F., Tieschky, M., Faber, S., Englmeier, K. H. & Reiser, M. Functional analysis of articular cartilage deformation, recovery, and fluid flow following dynamic exercise in vivo. *Anat. Embryol.* **200**, 419–424 (1999).
54. Sutter, E. G. et al. In vivo measurement of localized tibiofemoral cartilage strains in response to dynamic activity. *Am. J. Sports Med.* **43**, 370–376 (2015).
55. Liu, F. et al. In vivo tibiofemoral cartilage deformation during the stance phase of gait. *J. Biomech.* **43**, 658–665 (2010).
56. Van De Velde, S. K. et al. Increased tibiofemoral cartilage contact deformation in patients with anterior cruciate ligament deficiency. *Arthritis Rheum.* **60**, 3693–3702 (2009).
57. Kurz, B. et al. Biosynthetic response and mechanical properties of articular cartilage after injurious compression. *J. Orthop. Res.* **19**, 1140–1146 (2001).
58. Patwari, P., Cheng, D. M., Cole, A. A., Kuettner, K. E. & Grodzinsky, A. J. Analysis of the relationship between peak stress and proteoglycan loss following injurious compression of human post-mortem knee and ankle cartilage. *Biomech. Model. Mechanobiol.* **6**, 83–89 (2007).
59. Patwari, P. et al. Proteoglycan degradation after injurious compression of bovine and human articular cartilage in vitro: interaction with exogenous cytokines. *Arthritis Rheum.* **48**, 1292–1301 (2003).
60. Stolberg-Stolberg, J. A. et al. Effects of cartilage impact with and without fracture on chondrocyte viability and the release of inflammatory markers. *J. Orthop. Res.* **31**, 1283–1292 (2013).
61. Natoli, R. M., Scott, C. C. & Athanasiou, K. A. Temporal effects of impact on articular cartilage cell death, gene expression, matrix biochemistry, and biomechanics. *Ann. Biomed. Eng.* **36**, 780–792 (2008).
62. Guilak, F., Meyer, B. C., Ratcliffe, A. & Mow, V. C. The effects of matrix compression on proteoglycan metabolism in articular cartilage explants. *Osteoarthritis Cartilage* **2**, 91–101 (1994).
63. Ng, K. W. et al. Duty cycle of deformational loading influences the growth of engineered articular cartilage. *Cell. Mol. Bioeng.* **2**, 386–394 (2009).
64. Nam, J., Aguda, B. D., Rath, B. & Agarwal, S. Biomechanical thresholds regulate inflammation through the NF-κB pathway: experiments and modeling. *PLoS ONE* **4**, e5262 (2009).
65. Mauck, R. L., Nicoll, S. B., Seyhan, S. L., Ateshian, G. A. & Hung, C. T. Synergistic action of growth factors and dynamic loading for articular cartilage tissue engineering. *Tissue Eng.* **9**, 597–611 (2003).
66. Torzilli, P. A., Bhargava, M. & Chen, C. T. Mechanical loading of articular cartilage reduces IL-1-induced enzyme expression. *Cartilage* **2**, 364–373 (2011).
67. Chan, P. S. et al. Gene expression profile of mechanically impacted bovine articular cartilage explants. *J. Orthop. Res.* **23**, 1146–1151 (2005).
68. Ashwell, M. S. et al. Changes in chondrocyte gene expression following in vitro impaction of porcine articular cartilage in an impact injury model. *J. Orthop. Res.* **31**, 385–391 (2013).
69. Atkinson, T. S., Haut, R. C. & Altiero, N. J. An investigation of biphasic failure criteria for impact-induced fissuring of articular cartilage. *J. Biomech. Eng.* **120**, 536–537 (1998).
70. Fragomen, A. T., McCoy, T. H., Meyers, K. N. & Rozbruch, S. R. Minimum distraction gap: how much ankle joint space is enough in ankle distraction arthroplasty? *HSS J.* **10**, 6–12 (2014).
71. Sanchez-Adams, J., Leddy, H. A., McNulty, A. L., O'Conor, C. J. & Guilak, F. The mechanobiology of articular cartilage: bearing the burden of osteoarthritis. *Curr. Rheumatol. Rep.* **16**, 451 (2014).
72. Lafeber, F., Veldhuijzen, J. P., Vanroy, J. L. A. M., Huber-Bruning, O. & Bijlsma, J. W. J. Intermittent hydrostatic compressive force stimulates exclusively the proteoglycan synthesis of osteoarthritic human cartilage. *Br. J. Rheumatol.* **31**, 437–442 (1992).
73. Van Valburg, A. A., Van Roy, H. L. A. M., Lafeber, F. P. J. G. & Bijlsma, J. W. J. Beneficial effects of intermittent fluid pressure of low physiological magnitude on cartilage and inflammation in osteoarthritis. An in vitro study. *J. Rheumatol.* **25**, 515–520 (1998).
74. Slynarski, K., Walawski, J., Smigielski, R. & van der Merwe, W. Two-year results of the PHANTOM high flex trial: a single-arm study on the atlas unicompartmental knee system load absorber in patients with medial compartment osteoarthritis of the knee. *Clin. Med. Insights Arthritis Musculoskelet. Disord.* **12**, 1–7 (2019).
75. Jung, W. H. et al. Second-look arthroscopic assessment of cartilage regeneration after medial opening-wedge high tibial osteotomy. *Arthrosc. J. Arthrosc. Relat. Surg.* **30**, 72–79 (2014).
76. Slynarski, K. & Lipinski, L. Treating early knee osteoarthritis with the Atlas® Unicompartmental Knee System in a 26-year-old ex-professional basketball player: a case study. *Case Rep. Orthop.* **2017**, 1–5 (2017).
77. Spahn, G., Klinger, H. M., Harth, P. & Hofmann, G. O. Cartilage regeneration after high tibial osteotomy results of an arthroscopic study. *Z. Orthop. Unfall.* **150**, 272–279 (2012).
78. Bode, G. et al. Comparison of the efficiency of an extra-articular absorber system and high tibial osteotomy for unloading the medial knee compartment: an in vitro study. *Knee Surg. Sport. Traumatol. Arthrosc.* **25**, 3695–3703 (2017).
79. Slynarski, K., Walawski, J., Smigielski, R. & van der Merwe, W. Feasibility of the Atlas Unicompartmental Knee System Load Absorber in improving pain relief and function in patients needing unloading of the medial compartment of the knee: 1-year follow-up of a prospective, multicenter, single-arm pilot study (PHANTOM). *Clin. Med. Insights Arthritis Musculoskelet. Disord.* **10**, 1–9 (2017).
80. Bikle, D. D. & Halloran, B. P. The response of bone to unloading. *J. Bone Miner. Metab.* **17**, 233–244 (1999).
81. Marijnissen, A. C. A. et al. Ankle images digital analysis (AIDA): Digital measurement of joint space width and subchondral sclerosis on standard radiographs. *Osteoarthritis Cartilage* **9**, 264–272 (2001).
82. Pouders, C. et al. Prevalence and MRI-anatomic correlation of bone cysts in osteoarthritic knees. *Am. J. Roentgenol.* **190**, 17–21 (2008).
83. Tanamas, S. K. et al. The association between subchondral bone cysts and tibial cartilage volume and risk of joint replacement in people with knee osteoarthritis: a longitudinal study. *Arthritis Res. Ther.* **12**, R58 (2010).
84. van Dijk, C. N., Reilingh, M. L., Zengerink, M. & van Bergen, C. J. A. The natural history of osteochondral lesions in the ankle. *Instr. Course Lect.* **59**, 375–386 (2010).
85. Hwang, J. et al. Increased hydraulic conductance of human articular cartilage and subchondral bone plate with progression of osteoarthritis. *Arthritis Rheum.* **58**, 3831–3842 (2008).
86. Carrino, J. A., Blum, J., Parellada, J. A., Schweitzer, M. E. & Morrison, W. B. MRI of bone marrow edema-like signal in the pathogenesis of subchondral cysts. *Osteoarthritis Cartilage* **14**, 1081–1085 (2006).
87. Hunter, D. J. et al. Bone marrow lesions from osteoarthritis knees are characterized by sclerotic bone that is less well mineralized. *Arthritis Res. Ther.* **11**, R11 (2009).
88. Yazawa, M., Kishi, K., Nakajima, H. & Nakajima, T. Expression of bone morphogenetic proteins during mandibular distraction osteogenesis in rabbits. *J. Oral. Maxillofac. Surg.* **61**, 587–592 (2003).
89. Claes, L., Recknagel, S. & Ignatius, A. Fracture healing under healthy and inflammatory conditions. *Nat. Rev. Rheumatol.* **8**, 133–143 (2012).
90. Song, J. et al. Fak-Mapk, Hippo and Wnt signalling pathway expression and regulation in distraction osteogenesis. *Cell Prolif.* **51**, e12453 (2018).
91. Wiegant, K. et al. Evidence of cartilage repair by joint distraction in a canine model of osteoarthritis. *Arthritis Rheumatol.* **67**, 465–474 (2015).
92. McGonagle, D., Baboolal, T. G. & Jones, E. Native joint-resident mesenchymal stem cells for cartilage repair in osteoarthritis. *Nat. Rev. Rheumatol.* **13**, 719–730 (2017).
93. Jones, B. A. & Pei, M. Synovium-derived stem cells: a tissue-specific stem cell for cartilage engineering and regeneration. *Tissue Eng. Part B Rev.* **18**, 301–311 (2012).
94. Jones, E. A. et al. Synovial fluid mesenchymal stem cells in health and early osteoarthritis: detection and functional evaluation at the single-cell level. *Arthritis Rheum.* **58**, 1731–1740 (2008).
95. Chen, Y., Sun, Y., Pan, X., Ho, K. & Li, G. Joint distraction attenuates osteoarthritis by reducing secondary inflammation, cartilage degeneration and subchondral bone aberrant change. *Osteoarthritis Cartilage* **23**, 1728–1735 (2015).
96. Sánchez, M. et al. Combination of intra-articular and intraosseous injections of platelet rich plasma for severe knee osteoarthritis: a pilot study. *Biomed. Res. Int.* **2016**, 4868613 (2016).
97. Kouroupis, D., Sanjurjo-Rodriguez, C., Jones, E. & Correa, D. Mesenchymal stem cell functionalization for enhanced therapeutic applications. *Tissue Eng. Part B Rev.* **25**, 55–77 (2019).
98. Kania, K. et al. Expression of growth and differentiation factor 5 during joint repair and osteoarthritis. *Osteoarthritis Cartilage* **28**, S34 (2020).
99. Kania, K. et al. Regulation of Gdf5 expression in joint remodelling, repair and osteoarthritis. *Sci. Rep.* **10**, 157 (2020).
100. Leijten, J. C. H. et al. GREM1, FRZB and DKK1 mRNA levels correlate with osteoarthritis and are regulated by osteoarthritis-associated factors. *Arthritis Res. Ther.* **15**, R126 (2013).
101. Raghu, H. et al. CCL2/CCR2, but not CCL5/CCR5, mediates monocyte recruitment, inflammation and cartilage destruction in osteoarthritis. *Ann. Rheum. Dis.* **76**, 914–922 (2017).
102. Miotla Zarebska, J. et al. CCL2 and CCR2 regulate pain-related behaviour and early gene expression in post-traumatic murine osteoarthritis but contribute little to chondropathy. *Osteoarthritis Cartilage* **25**, 406–412 (2017).
103. Teunissen, M. et al. Knee joint distraction-induced shift from catabolic to anabolic state occurs after the distraction period. *Osteoarthritis Cartilage* **28**, S76–S77 (2020).
104. Jeon, O. H. et al. Senescence cell–associated extracellular vesicles serve as osteoarthritis disease and therapeutic markers. *JCI Insight* **4**, e125019 (2019).
105. ArthroSave. KneeReviver. https://www.arthrosave.com/ (2020).

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Competing interests
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Review criteria
To find studies involving KJD treatment in OA (summarized in Table 1), MEDLINE, EMBASE and Web of Science libraries were searched with the following terms: (distraction OR arthrodiatasis OR arthrodiastasis) AND (knee OR tibiofemoral OR tibiofibular), and were applied on title and abstract and, in Web of Science, Keywords+. Only full-text publications about clinical studies in which KJD with external fixation was applied and the primary outcomes were patient-reported outcomes and/or cartilage tissue restoration were included in Table 1. Studies that did not fully meet the criteria are discussed in the text where relevant. Ongoing unpublished studies were included based on personal communication with principal investigators.

A new immunometabolic perspective of intervertebral disc degeneration

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Abstract | Intervertebral disc (IVD) degeneration is a common finding on spine imaging that increases in prevalence with age. IVD degeneration is a frequent cause of low back pain, which is a leading cause of disability. The process of IVD degeneration consists of gradual structural change accompanied by severe alterations in metabolic homeostasis. IVD degeneration, like osteoarthritis, is a common comorbidity in patients with obesity and type 2 diabetes mellitus, two metabolic syndrome pathological conditions in which adipokines are important promoters of low-grade inflammation, extracellular matrix degradation and fibrosis. Impairment in white adipose tissue function, due to the abnormal fat accumulation in obesity, is characterized by increased production of specific pro-inflammatory proteins such as adipokines by white adipose tissue and of cytokines such as TNF by immune cells of the stromal compartment. Investigations into the immunometabolic alterations in obesity and type 2 diabetes mellitus and their interconnections with IVD degeneration provide insights into how adipokines might affect the pathogenesis of IVD degeneration and impair IVD function and repair. Toll-like receptor-mediated signalling has also been implicated as a promoter of the inflammatory response in the metabolic alterations associated with IVD and is thus thought to have a role in IVD degeneration. Pathological starvation, obesity and adipokine dysregulation can result in immunometabolic alterations, which could be targeted for the development of new therapeutics.

Low back pain (LBP) adversely affects people of all ages and socioeconomic groups, approximately 700 million individuals globally in similar proportions across all continents and cultures[1,2]. LBP interferes with quality of life and is the leading cause of disability, as well as being the most common reason for consulting a health-care provider worldwide[3,4]. LBP incurs great costs for society, being responsible for >30% of absences from work, causing considerable loss of productivity and increasing direct health-care costs[4].

LBP is a complex condition with multiple contributors to pain and disability, including biological, psychological and social factors[4,5]. LBP can arise from many causes, but intervertebral disc (IVD) degeneration has been identified as an important cause[6,7] However, IVD degeneration is not always associated with LBP[8,9]. Spinal degenerative diseases are associated with demographic factors that are increasingly prevalent in the population, including advanced age, obesity, poor diet and occupational risk factors. With ageing, which is one of the primary risk factors for LBP, overuse of and injury to the back over a long lifetime lead to degenerative changes in the IVD, gradually causing the loss of normal spine structure and function and ultimately resulting in pain and disability[10].

IVD degeneration results from a range of molecular, biochemical, cellular and anatomical alterations that arise from external insults, such as mechanical injury and metabolic perturbations, and that change over time[11]. It is possible that IVD degeneration is an adaptive response to these external insults, rather than a disease[4,11]. Nevertheless, the clinical manifestation is a disease, either objective, when observed by a physician, or subjective, when perceived by the patient. Altered cell nutrition as a result of structural alterations to the cartilaginous endplate (CEP), a thin layer of hyaline cartilage that lies between the vertebra and disc, is considered a main cause of IVD degeneration[12]. Bidirectional crosstalk between the IVD and the adjacent bone marrow determines the microenvironment and pathological progression[13,14]. Degradation of the disc extracellular matrix (ECM), and the consequent fibrosis that occurs in the IVD and in the subchondral bone following a cascade of cellular and molecular changes, leads to biomechanical failure of the IVD and surrounding structures[15]. IVD degeneration is thought to occur when the homeostatic balance of the disc environment is lost and a predominantly catabolic and hypoxic microenvironment and a senescent cell profile

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Key points

- Intervertebral disc (IVD) degeneration is a common comorbidity in patients with obesity and those with type 2 diabetes mellitus.
- Dysregulation of obesity-associated pro-inflammatory adipokines and high concentrations of circulating lipids promote a chronic state of low-grade inflammation and extracellular matrix degradation in the IVD.
- Insulin resistance, hyperglycaemia, adipokines, advanced glycation end products and microvascular alterations negatively affect the IVD metabolic environment in type 2 diabetes mellitus.
- Premature senescence, increased cellular apoptosis and altered autophagic mechanisms perpetuate a catabolic environment in the IVD.
- Therapeutic strategies aimed at counteracting dysregulated pro-inflammatory adipokine production could be effective for the treatment of IVD degeneration.

Adipokines
Cytokines derived from adipose tissue that have pleiotropic functions in energy metabolism, immunity and inflammation; most adipokines are augmented in obesity and contribute to the associated low-grade inflammatory state.

Adiposity
The quality or state of accumulating abnormal amounts of fat in the body, especially in the visceral compartment. Adiposity is associated with several secondary diseases, such as type 2 diabetes mellitus, hypertension, cardiovascular diseases, fatty liver and musculoskeletal diseases such as osteoarthritis and intervertebral disc degeneration.

develops in the IVD[16], with consequent immunometabolic alterations[17,18] (BOX 1).

IVD degeneration and osteoarthritis (OA) have important similarities. Traditionally, IVD degeneration has been considered a result of age-related 'drying and cracking' of the disc tissues associated with loss of proteoglycan content, which can lead to decreased intravertebral height. In addition, alterations to the CEP might impair the delivery of essential nutrients to the IVD and compromise disc–vertebra crosstalk, with bone marrow oedema playing an important role in the conversion from silent to symptomatic joint degeneration[14]. Similarly, OA has been considered as a 'wear and tear' disease of articular cartilage, but this outdated view has been challenged in the past two decades. There is increasing evidence of the involvement of low-grade inflammation and metabolic disturbances in both OA[19–23] and in IVD degeneration[24–26], shifting the focus of research to the immunometabolic features of disease pathophysiology and the severe alterations in metabolism[27].

In OA and IVD degeneration in the context of obesity, dysfunctional adipose tissue contributes to the creation of a catabolic and detrimental systemic and local environment. Systemic low-grade inflammation is fuelled by high concentrations of pro-inflammatory cytokines and adipokines as well as by high concentrations of sugars and circulating lipids that in turn impair the metabolism of articular chondrocytes and IVD cells[20,26]. Increasing clinical evidence suggests that obesity and type 2 diabetes mellitus (T2DM) are interrelated: obesity is associated with insulin resistance (a hallmark of T2DM) and is one of the main risk factors for T2DM as well as being highly prevalent in patients with the disease[28]. The term 'diabesity' describes the coexistence of both diseases in association with a state of chronic, low-grade inflammation[29,30]. Diabesity is characterized by considerable metabolic alterations, abnormal fat accumulation, dysfunction of white adipose tissue, altered glucose and lipid metabolism and inflammation[31], all of which strongly influence the development of IVD degeneration (FIG. 1). Indeed, IVD degeneration is more severe in patients with adiposity (overweight and obesity) than in patients with normal weight and normal fat mass accumulation[32]. Furthermore, a Mendelian randomization study determined that BMI has a causal effect on LBP and chronic back pain[33].

In this Review, we focus on the role of immunometabolic alterations that are involved in the pathogenesis of IVD degeneration, drawing on similarities between OA and IVD degeneration and summarizing the current state of knowledge about the role of adipokines in impaired metabolism in IVD cells. As evidence suggests that Toll-like receptors (TLRs) promote the inflammatory response in the metabolic alterations of IVD, their role in IVD degeneration is also discussed. In addition, we highlight opportunities for future research, such as the opportunity to target metabolic pathways and mediators therapeutically.

Metabolic consequences of IVD degeneration

The metabolic state of the IVD and of articular cartilage is intimately linked to the supply of oxygen and nutrients. Nutrients that support cells in the nucleus pulposus region (BOX 1) are supplied by the blood vessels at the IVD margins and diffuse through the ECM of the avascular disc to the nucleus pulposus cells[34]. IVD cells are acutely sensitive to glucose deprivation and lactate accumulation[35]; within the nucleus pulposus region, however, the notochordal cells that are gradually replaced by chondrocyte-like mature nucleus pulposus cells during development are fundamentally different in terms of their nutritional requirements and responses to nutrient deprivation: mature nucleus pulposus cells are far more sensitive to nutritional deprivation[36]. Nutrient supply pathways to the nucleus pulposus can be compromised with ageing[12] and with other comorbidities[34], including atherosclerosis, sickle cell anaemia, Caisson disease and Gaucher disease, all of which are associated with increased IVD degeneration[37,38]. Interruption of nutritional supply pathways by systemic and vascular diseases can have severe consequences for cell metabolism, cell survival, IVD degeneration and even IVD repair. Furthermore, changes in osmotic concentration and mechanical loading also occur in these diseases and are likely to influence IVD cell metabolism even further. Therefore, understanding the nutrition and metabolism

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Box 1 | **IVD anatomy and physiology in health and disease**

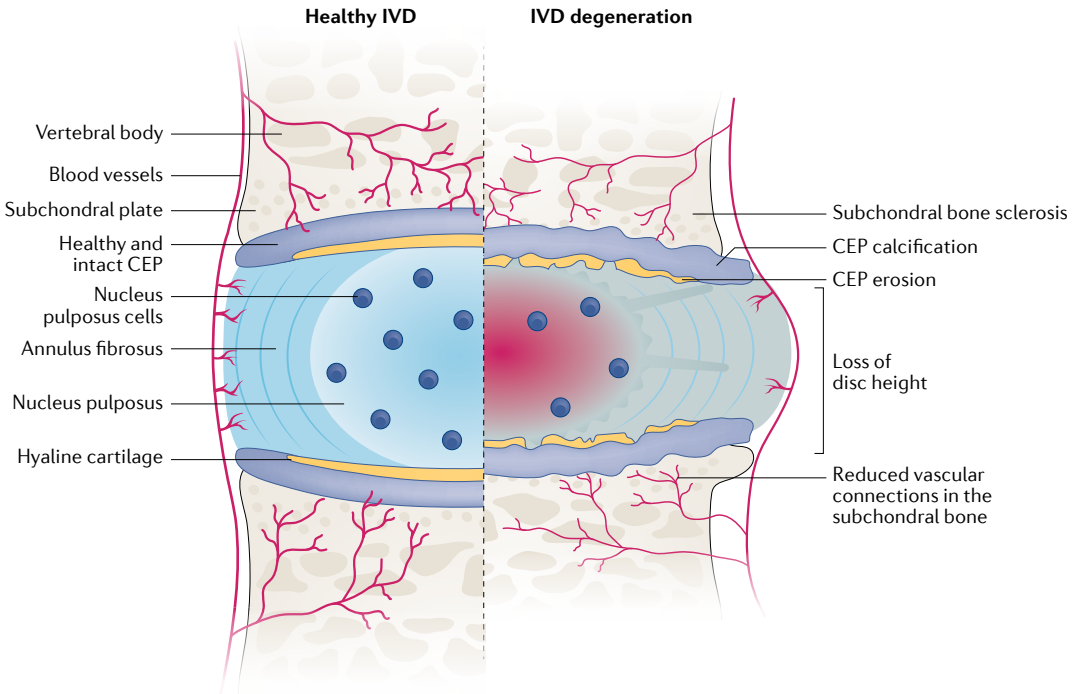
The intervertebral disc (IVD) is a shock-absorbing structure of the spine that has three main components: the inner nucleus pulposus, the outer annulus fibrosus and the cartilaginous endplates (CEPs), which anchor the disc to the adjacent vertebrae (see BOX 1 figure).

The nucleus pulposus is a gel-like, highly hydrated, proteoglycan-rich tissue. The healthy nucleus pulposus generates an intradiscal pressure that separates the two vertebrae, distributing pressure evenly over the two adjacent CEPs. The degenerated nucleus pulposus is an unorganized fibrous tissue that has largely lost its capacity to bind water under compression, resulting in a disc with greatly reduced height. Overall, the nucleus pulposus undergoes the most extensive structural alterations during IVD degeneration.

The healthy annulus fibrosus is a highly organized fibrous structure composed of concentric lamellae of tilted collagen fibres with scattered proteoglycans. In the degenerated IVD, the annulus fibrosus is severely deformed and accumulates structural defects such as axial fractures and edge lesions.

Healthy CEPs are hyaline cartilage structures of uniform thickness that do not protrude into the vertebrae. By contrast, in IVD degeneration, there is an enhancement in microscopic and macroscopic impairment to the CEP. Furthermore, there is a marked increase in the sclerosis of the subchondral bone, similar to degenerated cartilage in osteoathritis. These alterations to the CEP, as well as to the vertebral subchondral bone morphology, seem to precede IVD degeneration itself. Overall, the CEP can be regarded as a relevant structure of the disc because damage to the endplate is strongly related to both IVD degeneration and low back pain.

Globally, the degenerated IVD differs from its healthy counterpart in that disc height is substantially decreased or depleted owing to extracellular matrix depletion, a fibrous and dehydrated nucleus pulposus, severe structural modifications of annulus fibrosus collagen fibres, extensive CEP damage and sclerosis of the subchondral bone. Loss of disc height is a common finding on spine radiographs, and is an indicator of IVD degeneration, which is then followed up with more advanced MRI.



of IVD cells is important for the development of strategies to support sustained nutrient supply through the CEP and avoid the nutritional deprivation that is believed to accelerate IVD degeneration[39].

Considering the nutritional complexities of the IVD, it is essential to consider the consequent metabolic changes that occur along with the microenvironmental alterations in IVD degeneration. In the healthy IVD, the CEP is the main route through which essential nutrients diffuse from the peripheral vasculature to the nucleus pulposus[40]. Structural alterations to the CEP are thought to impair IVD cell nutrition, thus inducing cell death while simulating the effects of ECM degradation in the IVD[34]. The strong association between bony endplate damage and LBP has been demonstrated in population-based studies in the TwinsUK cohort[41,42]. MRI can reveal signal intensity changes — so-called Modic changes in bone adjacent to the CEP, characterized by inflammation, high bone turnover and fibrosis[14]. Biomarkers to distinguish silent versus symptomatic IVD degeneration are lacking, but Modic changes are highly specific for discogenic LBP. Bony endplate damage causes coupling between the disc and vertebra that affects the bi-directional transport of pro-inflammatory and pro-osteoclastic factors, which ultimately leads to the accumulation of damage and 'frustrated healing'[13]. Chronic stimulation of TLRs by ECM fragments leaking from degenerated discs facilitates the conversion of bone

Notochordal cells
Cells of mesodermal origin that form the notochord, a rod-like structure that is the principal longitudinal structural element of chordates and of the early embryo of vertebrates.

Bony endplate
A thin layer of porous bone, containing vessels, that is localized between the vertebral bone and cartilaginous endplate.

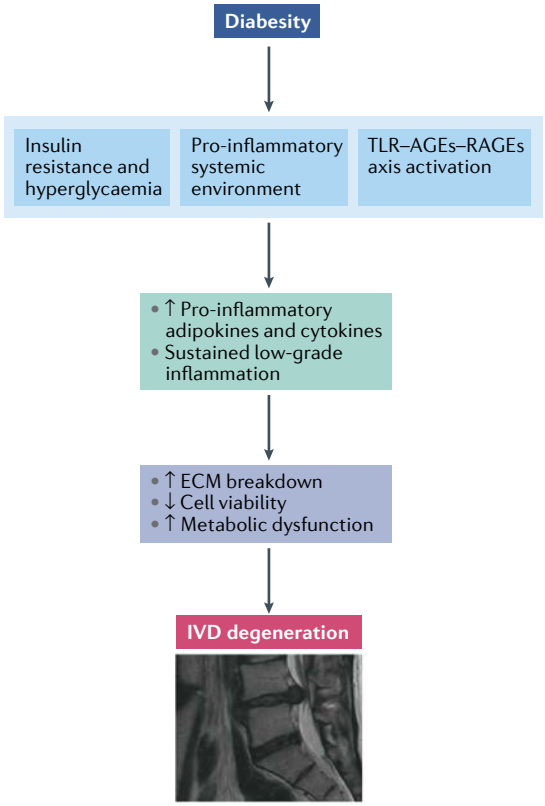


Fig. 1 | **Diabesity, low-grade inflammation and IVD degeneration.** Diabesity, which describes the co-occurrence of type 2 diabetes mellitus and obesity, results in a pro-inflammatory systemic environment that promotes insulin resistance, hyperglycaemia and increased production of adipokines, which, in turn, sustain the low-grade inflammation required for activation of Toll-like receptors (TLRs) and the interaction of advanced glycation end products (AGEs) with receptor for advanced glycation end products (RAGEs). These events activate multiple catabolic pathways that result in extracellular matrix (ECM) degradation, decreased cell viability and metabolic dysfunction at the cellular level, thus promoting intervertebral disc (IVD) degeneration. Spine image adapted from Sakai and Andersson[143], Springer Nature Limited.

Modic changes
Degenerative bone marrow changes seen in the vertebrae on MRI, with type 1 changes appearing as fibrovascular changes (mainly oedema and inflammation) in subchondral bone marrow, type 2 changes representing the conversion of yellow bone marrow to fat and type 3 changes appearing as highly mineralized, sclerotic bone.

Spinal motion segments
Functional spinal units that represent the focus of biomechanical functioning of the spine, consisting of two adjacent vertebrae, the intervertebral disc and all adjoining ligaments.

marrow to fat, as seen in Modic changes[14]. Therefore, understanding the metabolic changes in the IVD, especially in the CEP, should have a great influence on the development of regenerative and therapeutic strategies for the IVD.

Obesity, adipokines and IVD degeneration

Clinical evidence

Increasing evidence implicates increased body weight and elevated BMI as risk factors for the development of IVD degeneration[33,43,44]. Cross-sectional analysis directly associates high BMI with disc space narrowing and severity of lumbar IVD degeneration[32]; nevertheless, correlations with sex are somehow contradictory[45,46]. Overweight seems to affect IVD degeneration more profoundly than age or sex[47], as young individuals with obesity have a greater risk of IVD degeneration than those who develop obesity in middle age (40–45 years old)[48]. Single nucleotide polymorphisms (SNPs) associated with obesity and fat mass, namely SNPs rs11076008 and rs1121980, correlate with the onset of IVD degeneration and have been proposed as potential diagnostic and prognostic biomarkers for IVD degeneration[49,50]. However, some studies failed to correlate BMI, fat mass percentage or fat distribution with LBP or progression of IVD degeneration[51,52].

Adipokines

Excessive body weight determines the application of cumulative and repetitive forces on spinal motion segments, in particular in the lumbar spine, that can modify IVD biomechanics and thus favour IVD degeneration. Aside from abnormal mechanical overloading, the dysregulated production of adipokines by adipose tissue in obesity is now recognized as an important contributor to the metabolic and pro-inflammatory pathophysiological pathways affecting IVD homeostasis[26]. Adipokines (TABLE 1), initially described as regulators of energy metabolism, are nowadays recognized as crucial players in the immune system and the inflammatory response[53,54]. Thus, these low-molecular-weight, biologically active peptides contribute to chronic, obesity-associated, low-grade inflammation, and are implicated in augmented cell apoptosis, autophagy and ECM breakdown in IVD degeneration[24,44] (FIG. 2). Most published studies have focused on the identification of adipokine receptors, activated signalling pathways and cellular proteome changes in IVD. However, this research has largely been limited to cells and/or tissues from animal models or patients undergoing surgery, and data on clinical aspects, such as IVD degeneration in MRI, are scarce[26]. Also, as far as we are aware, the correlation between circulating concentrations of adipokines and their local levels in the spines of patients with IVD degeneration has not been analysed. However, several lines of evidence showed that annulus fibrosus and nucleus pulposus cells, cultured in vitro, secrete considerable levels of adipokines. Thus, IVD tissues produce adipokines that might affect cell function[25,26]. Further characterization of adipokine molecular signalling pathways and their multifaceted effects on the aetiology and development of IVD degeneration will lead to a more thorough understanding of the disease pathogenesis, supporting the development of much needed new therapeutic approaches to IVD degeneration.

The current understanding of the mechanisms by which adipokines contribute to inflammatory and metabolic processes in IVD degeneration are summarized in the following sections and in TABLE 2.

Leptin

Owing to the broad expression of leptin receptor (LEP-R; also known as obesity receptor (Ob-R)) in peripheral tissues, leptin, encoded by *LEP* (also known as *ob*), has pleiotropic activity in physiological and pathological states and has been identified as a cornerstone molecule in the interplay between metabolism and the immune system[53]. Initially described as a metabolic sensor that controls appetite and body weight homeostasis, leptin also regulates inflammation, infection, bone and cartilage homeostasis, insulin secretion, thermogenesis, lipid

Table 1 | **Overview of adipokines**

Adipokine name	Description	Signalling	Functions	Refs
Leptin	Non-glycosylated cytokine-like hormone of 16 kDa encoded by *LEP* (also known as the obese gene (*ob*)) Mainly produced by white adipose tissue, but also by the brain, placenta, skeletal muscle, intestines, bone and joint tissues	LEP-R, encoded by *LEPR*, exists in at least six isoforms (one soluble, four short and one long), which differ in the length of their cytoplasmatic domain Canonical activation of the LEP-R long isoform by leptin is mediated through JAK–STAT signalling; alternative pathways include ERK1/2, JNK, p38 MAPK, PKC or PI3K/Akt signalling	Crucial in appetite and body weight homeostasis, via central signalling at the hypothalamus Has also been implicated in insulin secretion, lipid homeostasis, thermogenesis, reproductive functions, angiogenesis, infection, inflammation and homeostasis of bone and cartilage	53
Adiponectin	Also known as ACRP30 244-aa adipokine encoded by *ADIPOQ* Structurally homologous to complement factor C1q, collagen VIII and collagen X Produced mainly by adipose tissue but also by skeletal muscle, bone marrow and cardiac tissue Found in several molecular configurations (trimers, hexamers and 12–18-monomer forms)	Specific receptors AdipoR1 (prevalent in skeletal muscle) and AdipoR2 (mainly present in the liver) Signal transduction involves AMPK, PPARα or PPARγ pathways	Increases fatty acid oxidation and glucose uptake in the muscle and reduces the synthesis of glucose in the liver, and is implicated in metabolic syndrome, cardiovascular complications, osteoarthritis and rheumatoid arthritis	67
Resistin	Also known as ADSF or cysteine-rich secreted protein (FIZZ3) Cysteine-rich 12.5 kDa protein found as dimers in human blood Highly expressed in mononuclear leukocytes, macrophages, spleen and bone marrow cells	No specific receptor has been described, but TLR4 was shown to mediate the resistin-induced secretion of pro-inflammatory cytokines (IL-12, IL-6 and TNF), probably via C/EBPβ and NF-κB	Has been described as a link between obesity and diabetes by promoting insulin resistance Seems to be involved in musculoskeletal disease pathology by modulating angiogenesis and inflammatory environment within the joint	73,74,134
Visfatin	Also known as NAMPT or PBEF Homodimeric 52 kDa cytokine-like peptide that has both extracellular (eNAMPT) and intracellular (iNAMPT) forms	Acts as the rate-limiting enzyme in the biosynthesis of NAD from nicotinamide No specific receptor has been described	Likely to be involved in cell differentiation, stress response and apoptosis Function is still ill-defined, but evidence suggests it has activity in metabolic pathological conditions, inflammation and musculoskeletal diseases	135
Lipocalin-2	Also known as neutrophil gelatinase-associated lipocalin Multifunctional 25 kDa glycoprotein expressed in white adipose tissue as well as in kidney, human neutrophil granules, immune cells, spleen, liver and chondrocytes	Mouse lipocalin-2 binds to the transporter protein SLC22A17 (24p3R), whereas human lipocalcin-2 binds to megalin/glycoprotein GP330, an LDL receptor	Has regulatory roles in haematopoietic cells apoptosis, immune system response and metabolic homeostasis. Also described as a sensor of mechanical load and inflammatory status of the joint	79
Progranulin	Also known as proepithelin, PC-cellderived growth factor, granulinepithelin precursor or acrogranin 68–88-kDa cysteine-rich secreted glycoprotein that can be proteolytically cleaved into homologous subunits, in particular granulins and epithelins Lately recognized as an adipokine, progranulin is also produced by macrophages, epithelial cells and chondrocytes	Directly interacts with TNF receptors, with greater affinity than TNF for TNFR2 (linked to immunosuppressive effects), but comparable with TNF in binding affinity for TNFR1 (associated with pro-inflammatory activity)	Implicated in inflammation, wound healing, obesity and rheumatic diseases	136
Ghrelin	28-residue peptide hormone mainly secreted by the stomach's oxyntic glands, but also expressed in lung, hypothalamus, ovary, testis and pancreatic islets	Signals via GHS-R	Stimulates food intake and adiposity and regulates glucose metabolism, gut motility, reward behaviour and the immune system, as well as bone and cartilage metabolism, proliferation and differentiation. Plasma concentrations of ghrelin and LEAP-2 (a recently discovered endogenous antagonist of GHS-R) correlate with rheumatoid arthritis pathology	89,137,138

Table 1 (cont.) | **Overview of adipokines**

Adipokine name	Description	Signalling	Functions	Refs
Omentin	Also known as intelectin-1 40-kDa protein secreted by omental adipose tissue and highly abundant in human plasma Newly identified type of calcium-dependent lectin	Has affinity for galactofuranosyl residues (constituents of pathogens and dominant immunogens)	Suggested to have an important role in the innate immune response to parasite infection, through specific recognition of pathogens and bacterial components Also implicated in obesity, asthma and Crohn's disease	139,140
Vaspin	Also known as serpin A12 or visceral adipose-specific serpin 45-kDa single peptide with a hydrophobic N terminus belonging to the serine protease inhibitor family Newly identified adipokine	Has insulin-sensitizing effects	Might provide a compensatory response to obesity and its inflammatory complications Also associated with glycolipid metabolism, blood pressure, apoptosis, diabetes mellitus and atherosclerosis	140
Apelin	Endogenous peptide encoded by *APLN* and expressed as a 77-amino acid prepropeptide, which is then cleaved into a mature apelin peptide (apelin-36) or a family of shorter peptides (apelin-17, apelin-12 and apelin-13), which have more potent functionality than apelin-36; a pyroglutamyl form of apelin-13 also showed high activity	Ligand for the orphan G protein-coupled receptor APJ, which is closely related to the angiotensin receptor	Expression of apelin in adipose tissue is increased by TNF, and it might act as a pro-inflammatory adipokine that contributes to vascular wall inflammation	141
Chemerin	Also known as retinoic acid receptor responder protein 2 (RARRES2) or TIG2 Secreted as an inactive precursor, prochemerin, which is activated by proteolytic C-terminal cleavage by neutrophil-derived proteases (elastase and cathepsin G), mast cell products (tryptase), proteases of the coagulation cascade and certain bacterial proteases at the inflammatory site	Strong chemotactic adipokine that binds to chemokine-like receptor 1 Two other receptors for this adipokine have been described, CCRL2 and GPR1, but their functional relevance is largely unknown	The chemerin–ChemR23 signalling pathway could serve as a bridge between innate and adaptive immunity, as ChemR23 is expressed primarily by antigen-presenting cells (e.g. dendritic cells), natural killer cells and macrophages	142

ADSF, adipose tissue-specific secretory factor; AMPK, AMP-activated protein kinase; GHS-R, growth hormone secretagogue receptor type 1; LEAP-2, liver-enriched antimicrobial peptide-2; LEP-R, leptin receptor; NAD, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; PBEF, pre-B cell colony-enhancing factor 1; PPAR, peroxisome proliferator-activated receptor; TLR4, Toll-like receptor 4.

homeostasis, angiogenesis and reproductive functions[53]. Both leptin and its receptor have been identified in IVD tissues, with increased expression in degenerated discs[55–57]. Local expression of leptin is increased in the posterior compared with the anterior annulus fibrosus, and it is produced by 3D cultured annulus fibrosus cells, highlighting the presence of a local autocrine or paracrine regulatory system in IVD[55,58]. Since its discovery in the IVD, leptin has been implicated in disc cell proliferation, cytoskeletal remodelling and proteome alterations, namely augmenting catabolic and pro-inflammatory mediators of ECM degradation. CEP calcification and degenerative mechanisms in adjacent connective tissues associated with IVD are also influenced by leptin[26].

Leptin augments annulus fibrosus and nucleus pulposus cell proliferation via induction of cyclin D1 and activation of PI3K–Akt, JAK–STAT3 and MEK–ERK signalling transduction pathways[57]. These proliferating cells demonstrate deficient ECM synthesis owing to increased ECM expression of proteolytic enzymes, which contributes in part to the disc cell senescence that underlies IVD degeneration[56,57]. The observation that leptin also induces the expression and organization of cytoskeletal proteins, namely β-actin and F-actin stress fibres, in nucleus pulposus cells through Rho–ROCK–LIMK–cofilin signalling also provides novel insights into the role of leptin in IVD degeneration[59,60].

In bovine and rat disc cells (annulus fibrosus and nucleus pulposus cells), leptin, alone or in synergy with IL-1β, IL-6 or TNF, increases the production of nitric oxide and the expression of both pro-inflammatory cytokines (IL-6 and TNF) and ECM-degrading enzymes (namely the matrix metalloproteinases MMP-1, MMP-3, MMP-7, MMP-9, MMP-11 and MMP-13, ADAMTS-4 and ADAMTS-5)[61,62]. The activation of JAK2–STAT3, ERK, JNK, and p38 MAPK signalling pathways is involved in leptin-induced expression of MMP-1 and MMP-13 expression. Furthermore, in nucleus pulposus cells, leptin downregulates aggrecan levels (at both the mRNA and protein levels) through the p38 MAPK–ADAMTS pathway[63]. Thus, leptin leads to an imbalance favouring catabolic degradative processes, together with a decrease in hydrostatic pressure and an increase in

Cyclin D1
A protein that regulates cell-cycle progression through the G1 to S phase transition.

shear forces owing to decreased proteoglycan synthesis, all of which contribute to progressive IVD degeneration.

In a rat model of lumbar disc degeneration, leptin is co-expressed in the CEP with markers of CEP calcification and chondrocyte hypertrophy. In particular, leptin increases expression of the osteogenic factors RUNX2 and osteocalcin in a dose-dependent and time-dependent manner, and promotes the mineralization of CEP cells via activation of STAT3 and ERK1–ERK2 signalling pathways[64]. Calcification of the CEP limits nutrient supply and can thus impair disc cell activity and viability. Leptin also induces terminal differentiation of annulus fibrosus cells, as assessed by expression of collagen X and MMP-13, through p38 MAPK and ERK1–ERK2 signalling but not through JNK1–JNK2 pathways[65]. In IVD-adjacent tissues, leptin expression is increased in ligamentum flavum tissue of patients with lumbar spinal stenosis, and promotes expression of IL-6 (one of the key mediators of low-grade inflammation) and type I and III collagens in the ligamentum flavum, being positively correlated with its hypertrophy and fibrosis[66].

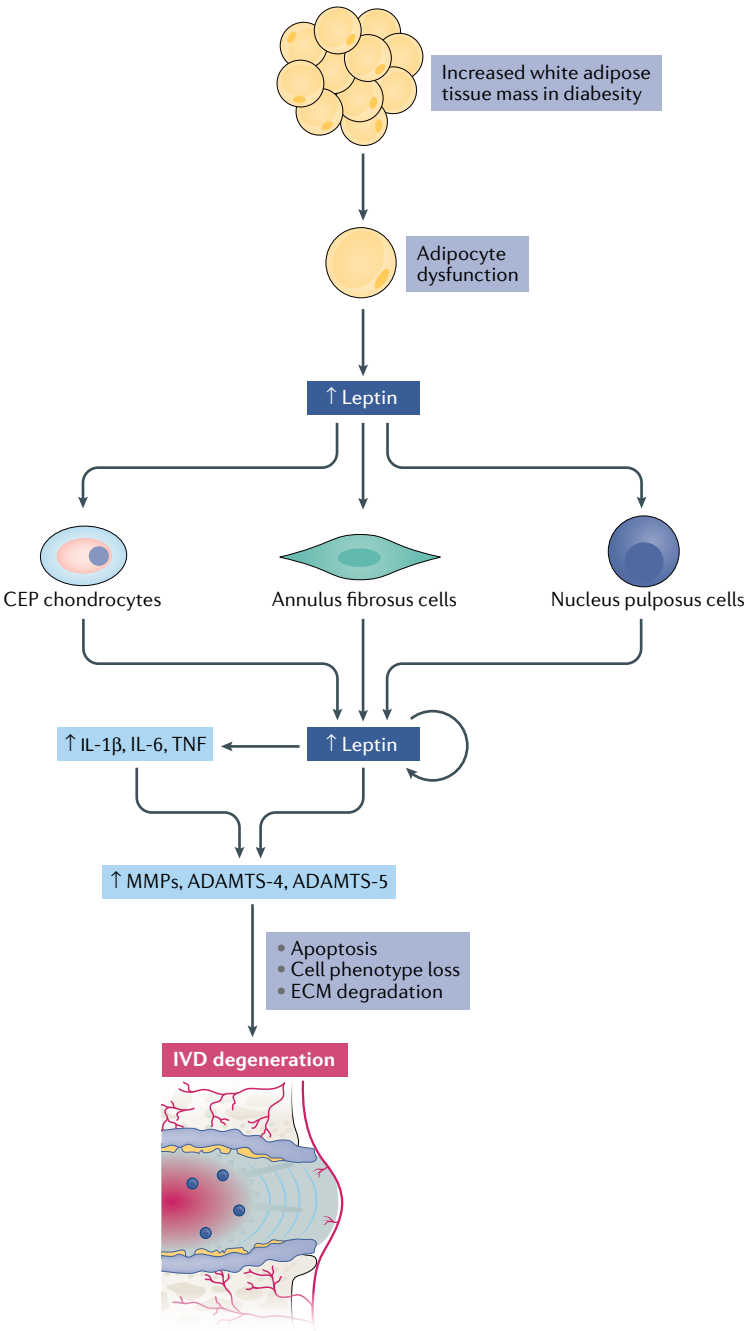


Fig. 2 | **Adipokines involved in low-grade inflammation and metabolic responses in IVD degeneration.** Increased white adipose tissue mass in diabesity results in adipocyte dysfunction, in the form of immunometabolic alterations that increase the production and secretion of leptin. Leptin, as a prototypical adipokine, contributes to catabolic effects on the cells within the nucleus pulposus, annulus fibrosus and cartilaginous endplate (CEP), promoting the production and secretion of more leptin and the pro-inflammatory cytokines IL-1β, TNF and IL-6 by these cells. Consequently, concentrations of the matrix metalloproteinases MMP-1, MMP-3, MMP-7, MMP-9, MMP-11, MMP-13 and ADAMTS-4 and ADAMTS-5 genes are increased, resulting in extracellular matrix (ECM) degradation, apoptotic cell death and loss of differentiated disc cell function, all of which contribute to disc degeneration. IVD, intervertebral disc.

Adiponectin. Patients with morbid obesity and those with obesity-associated metabolic disease tend to have diminished circulating concentrations of adiponectin, which are restored following weight loss or treatment with the peroxisome proliferator-activated receptor-γ (PPARγ) agonists thiazolidinediones[67]. Specific binding of adiponectin to its receptors AdipoR1 and AdipoR2 enhances insulin sensitivity via AMP-activated protein kinase (AMPK) and modulates fatty acid and glucose metabolism through AMPK, calcium ion and PPARα[68]. Thus, adiponectin has recognized activity in metabolic syndrome and T2DM as well as in the function of immune cells and in cartilage and bone metabolism[69].

Although adiponectin is associated with IVD degeneration, conflicting results in the published literature call into question whether it has a protective or a degenerative influence. Circulating concentrations of adiponectin were reported to be increased in patients with lumbar IVD degeneration[70], but a subsequent study indicated that adiponectin is downregulated in nucleus pulposus cells from degenerated human IVD compared with healthy tissue, and adiponectin concentrations in IVD tissue correlated negatively with the severity of IVD degeneration[71]. Differences in adiponectin sources and tissue samples could contribute to such discrepancies. Because IVD tissue is mainly avascular, the serum concentration of adiponectin is likely to be poorly related to its local levels in the IVD. Adiponectin downregulation in the IVD could be related to decreased viability of nucleus pulposus cells or impaired protein synthesis in senescent cells, and could lead to an IVD degeneration-associated inflammatory response[71]. The secretion of adiponectin by both healthy and degenerated nucleus pulposus cells points to the presence of a local paracrine regulatory system[71]. Published data on adiponectin receptors are also contradictory. Whereas one study reported a gradual reduction of AdipoR1 and AdipoR2 expression with increased severity of IVD degeneration[72], another found their expression increased in degenerated IVD tissues and nucleus pulposus cells, probably attributable to a compensatory mechanism to enhance tissue sensitivity to adiponectin in response to low levels of adiponectin expression[71].

Table 2 | **Adipokines involved in low-grade inflammation and metabolic responses in IVD degeneration**

Adipokine	Effects on NP cells	Effects on AF cells	Effects on CEP cells
Leptin	Expression of functional LEP-R ↑ Cell proliferation ↑ Proteolytic enzyme synthesis ↑ NO production ↓ Aggrecan levels	Expression of functional LEP-R ↑ Cell proliferation ↑ NO production Induces terminal differentiation of AF cells	↑ RUNX2 and osteocalcin Regulates CEP degeneration and ossification through activation of MAPK–ERK signalling
Progranulin	Engineered analogue (atsttrin) inhibits TNF-induced expression of iNOS, COX2, IL-6, IL-17 and MMP-13	↑ Concentrations of MMP-13 and ADAMTS-5 ↑ iNOS expression ↑ Activation of NF-κB and Wnt–β-catenin signalling	↑ Concentrations of MMP-13 and ADAMTS-5 ↑ iNOS expression ↑ Activation of NF-κB and Wnt–β-catenin signalling
Adiponectin	Conflicting evidence of functional AdipoR1 and AdipoR2 expression ↓ Expression in degenerated NP cells ↓ Secretion of TNF	↓ TNF secretion	NR
Visfatin	High concentrations in NP cells with severe degeneration Expression increased by IL-1β Regulates autophagy via LC3-I, LC3-II and beclin-1	NR	NR
Resistin	↑ Concentration with IVD degeneration ↑ Expression of ADAMTS-5 and CCL4, thereby increasing macrophage attraction	Low levels in healthy discs increasing with degeneration	NR
Lipocalin-2	NR	Concentration increased by nerve growth factor (in rat AF cells), which blocks MMP-9 autodegradation	NR
Ghrelin	Counteracts the catabolic effects of IL-1	NR	NR

AF, annulus fibrosus; CEP, cartilaginous endplate; COX2, cyclooxygenase 2; iNOS, inducible nitric oxide synthase; IVD, intervertebral disc; LEP-R, leptin receptor; NO, nitric oxide; NP, nucleus pulposus; NR, not reported.

Adiponectin decreased TNF production and secretion in a time-dependent and dose-dependent manner, both in human degenerated nucleus pulposus cells and in IL-1β-stimulated nucleus pulposus and annulus fibrosus cells from rats, with no effect on IL-1β-induced IL-6 expression. By repressing the production and release of pro-inflammatory cytokines, adiponectin might contribute to the re-establishment of disc homeostasis and protect the IVD from degeneration[71,72].

Resistin. The dimeric cysteine-rich adipokine resistin promotes insulin resistance and expression of pro-inflammatory mediators via TLR4 binding[73–75]. Resistin concentrations are low in healthy discs and increase during IVD degeneration in a dose–response relationship with the severity of IVD degeneration[76]. Resistin acts in a dose-dependent and time-dependent manner to enhance ADAMTS-5 expression in rat nucleus pulposus cells through activation of the p38 MAPK pathway[77], and in degenerated human nucleus pulposus tissue resistin promotes the expression of CCL4 (also known as macrophage inflammatory protein-1β) by binding to TLR4 (REF.[76]). Resistin-induced CCL4 expression occurs via stimulation of p38 MAPK (but not JNK or ERK) and p65 phosphorylation with consequent NF-κB activation and promotion of CCL4 gene expression, which is required for resistin-induced macrophage attraction by rat nucleus pulposus cells[76]. Thus, the promotion of expression of metalloproteinases and pro-inflammatory mediators, together with macrophage infiltration, could lead to resistin-mediated IVD degeneration.

Visfatin. The homodimeric cytokine-like enzyme visfatin (nicotinamide phosphoribosyltransferase), which limits the biosynthesis of nicotinamide adenine dinucleotide (NAD) from nicotinamide and is likely to be involved in cell differentiation, stress response and apoptosis, is present at increased concentrations in metabolic diseases and inflammation[75]. Visfatin concentrations in nucleus pulposus tissues from IVDs with moderate-to-severe degeneration are higher than in IVDs with less extensive degeneration, strongly indicating a correlation between visfatin concentration and disease severity[78]. Visfatin expression is dose- and time-dependently increased by IL-1β in nucleus pulposus cells. Administration of the visfatin inhibitor APO0866 and knockdown of visfatin expression with short hairpin RNA reveals that visfatin is involved in the IL-1β-induced upregulation of the ECM-degrading enzymes ADAMTS-4, ADAMTS-5 and MMP-13, and downregulation of the ECM proteins

Ligamentum flavum
One of a series of ligaments of yellow elastic tissue connecting the laminae of adjoining vertebrae from the axis to the sacrum, forming the posterior wall of the spinal canal.

Metabolic syndrome
A condition characterized by three or more metabolic risk factors (including abdominal obesity, hypertension, dyslipidaemia and insulin resistance) and that is linked to an increased risk of the development of type 2 diabetes mellitus and cardiovascular disease.

aggrecan and collagen II[78]. Visfatin inhibition also induces nucleus pulposus cell autophagy by increasing the conversion of MAP1A/MAP1B LC3 B (LC3-I) to MAP1A/MAP1B LC3 A (LC3-II) and the expression of beclin-1. Interestingly, inhibition of autophagy blocks the effects of visfatin inhibition on ECM protein expression. Hence, visfatin inhibition has been proposed as a potential therapeutic approach to protecting nucleus pulposus cells from ECM degradation and apoptosis, via autophagy[78].

Lipocalin-2. Through binding to the Gram-negative bacteria siderophore enterobactin, lipocalin-2 (also known as neutrophil gelatinase-associated lipocalin) depletes iron stores and exerts bacteriostatic effects. This glycoprotein has also been implicated in apoptosis of haematopoietic cells, metabolic homeostasis and inflammatory and immune system disorders[79]. Even though it has potential as a biomarker of rheumatic disease, the role of lipocalin-2 in IVD degeneration has been underexplored. In rat annulus fibrosus cells, nerve growth factor (NGF) augments expression of lipocalin-2, which blocks MMP-9 auto-degradation via the formation of stable covalent complexes. Accordingly, NGF stimulation increases MMP-9 protein expression but not *Mmp9* gene expression in annulus fibrosus cells[80,81], suggesting that NGF acts by activating pre-existing MMP-9 and increases the stability of the protein.

Progranulin. Intact progranulin has well-recognized anti-inflammatory activity via its binding to TNF receptors, whereas the products of its enzymatic proteolysis, namely granulins, have pro-inflammatory properties[82]. Because progranulin binds to TNF receptor 1 (TNFR1) (linked with pro-inflammatory effects) with an affinity similar to that of TNF, and has a higher affinity than TNF for TNFR2 (associated with immunosuppressive action), this cysteine-rich glycoprotein antagonizes the deleterious activities of TNF. Thus, the synthesis of the engineered progranulin-derived protein atsttrin could provide a new therapeutic strategy in the management of rheumatic diseases[82,83].

Progranulin concentrations are elevated in peripheral blood sera and disc tissues of patients with IVD degeneration, and correlate with clinical symptoms[84]. In addition, progranulin co-localizes with activated macrophages and microglia in spinal cord contusions[85]. Progranulin expression is also upregulated in the disc tissue of mice during the ageing process[86]. The mechanisms of action of progranulin in IVD degeneration pathophysiology were nicely revealed in progranulin knockout mice, with effects such as disordered bone metabolism, aggrecan degradation and increased concentrations of MMP-13 and ADAMTS-5, proteoglycan loss in annulus fibrosus and CEP tissues, increased gene and protein expression of inducible nitric oxide synthase (iNOS), and increased activation of NF-κB and Wnt–β-catenin signalling. Enhanced catabolism in *Pgrn*$^{-/-}$ mice leads to dysfunction in annulus fibrosus and CEP tissues, which substantially affects nutrient diffusion to the nucleus pulposus and accelerates IVD degeneration[86]. Progranulin could also reduce TNFR1-induced production of IL-17 with a consequent decrease in recruitment of T helper 17 cells, and could increase IL-10 production and anti-inflammatory activity via TNFR2 activation[84]. The protective role of progranulin in IVD degeneration is strengthened by evidence that TNF-induced expression of iNOS, cyclooxygenase-2, IL-6, IL-17 and MMP-13 in human nucleus pulposus cells is inhibited by atsttrin, which has been proposed as a new candidate drug for disc degeneration[87].

Ghrelin. Ghrelin is produced mainly in the oxyntic glands of the stomach. Acting via growth hormone secretagogue receptor type 1 (GHS-R), ghrelin induces the secretion of growth hormone and regulates food intake, gastrointestinal tract motility, adiposity, glucose metabolism, the reproductive axis and anti-inflammatory processes[88–90]. Ghrelin is expressed in tissues and cells harvested from living tissues (primary cells) of human nucleus pulposus and its expression in these cells is downregulated by IL-1β[91]. Ghrelin counteracts IL-1β-induced catabolism, inflammation (namely expression of ADAMTS-5, MMP-13, iNOS and TNF), apoptosis and disorganized proliferation in human primary nucleus pulposus cells and attenuates the expression of MMP-13, ADAMTS-4 and ADAMTS-5 in a rabbit model of IVD degeneration[91]. Ghrelin-mediated protection against IVD degeneration is also supported by the induction of aggrecan, collagen-II and Sox-9 proteins via GHS-R in the rabbit model. Ghrelin also acts via inhibition of the NF-κB signalling pathway by reducing IκB phosphorylation and p65 nuclear translocation and by inducing Akt signalling, which is involved in the anabolic activity of ghrelin in nucleus pulposus cells[91].

T2DM and IVD degeneration

Clinical evidence

The results of several cross-sectional and retrospective studies implicate T2DM as a risk factor for IVD degeneration that correlates with the severity of degeneration[43,44]. In particular, in the Wakayama Spine study, which involved a large, longitudinal population-based cohort, T2DM was associated with IVD degeneration in the upper lumbar spine[92]. Long-standing and poorly controlled T2DM is also associated with the severity of IVD degeneration[93]. T2DM has also been associated with spinal stenosis, osteoporotic vertebral fractures and IVD herniation[43]. Nevertheless, some researchers correlate IVD degeneration only with T2DM-associated risk factors, such as BMI, age or high levels of LDL cholesterol, but not with T2DM itself[94–96]. Given the vast heterogeneity and differences in the primary objectives of published studies, the causal relationships between T2DM and IVD degeneration are sometimes inconsistent or elusive; therefore, well-designed multicentre clinical studies are needed[43].

Pathophysiological mechanisms

Obesity is the main risk factor for the development of T2DM; therefore, both chronic inflammation and deregulation of adipokine concentrations could contribute to IVD degeneration in patients with T2DM. Nevertheless, preclinical evidence from studies in a rat

model of polygenic obesity and T2DM suggests that T2DM, but not obesity, compromises IVD composition, ECM homeostasis and biomechanical behaviour[97], indicating the involvement of obesity-independent mechanisms in T2DM-induced IVD degeneration. T2DM is a highly prevalent metabolic disease characterized by insulin resistance, hyperinsulinaemia, and irreversible formation and accumulation of advanced glycation end products (AGEs) as an outcome of hyperglycaemia (see FIG. 1). These biochemical alterations follow pathophysiological changes in the bony endplate and CEP and contribute to undermining the nutrient supply, cell viability, matrix homeostasis and biomechanical properties of the IVD, leading to structural weakening and, ultimately, IVD degeneration[43] (BOX 2).

Bony endplate changes. As the intermediary bed between the vertebra and disc, the bony endplate and CEP provide a passageway for blood, nutrients and metabolic waste moving to and from the nucleus pulposus and inner annulus fibrosus tissues of the avascular disc[98]. Reduced CEP permeability and microvascular density compromises IVD nutrition and hampers cell metabolism and biosynthetic function, thus causing or accelerating IVD degeneration[98].

Given the anabolic activity of insulin on bone[99], T2DM-associated hyperinsulinaemia induces an increase in bone mineral density and osteoblast activity that contributes to bony endplate sclerosis. Concurrently, increased oxidative stress and AGEs derived from T2DM-related hyperglycaemia cause narrowing of the bony endplate microvessels and result in a reduction of microvasculature density[100]. Both endplate sclerosis and vascular injury limit blood flow as well as the passage of nutrients to IVD cells, thereby compromising disc nutrition and the removal of metabolic waste, inflammatory mediators and toxins, with adverse effects on the activity and viability of IVD cells[43,97,101,102].

Cellular apoptosis, senescence and autophagy. The IVD nutrient deprivation and hyperglycaemia observed in T2DM represent cellular stress stimuli that trigger death receptors, as well as endoplasmic and mitochondrial apoptosis pathways, in IVD cells[102–104]. Elevated concentrations of glucose also trigger production of reactive oxygen species, mitochondrial damage and stress-induced premature senescence in annulus fibrosus, nucleus pulposus and notochordal cells[105–107]. Cell senescence diminishes the potential to replace necrotic and apoptotic IVD cells, leading to a net reduction in metabolically active cells and ECM turnover, which implies a shift towards catabolic ECM degradation, structural failure and the probable development of IVD degeneration[43,108]. Counteracting T2DMs-induced IVD cell senescence and death, hyperglycaemia augments cell autophagy markers, probably as a protective mechanism[102]. Nevertheless, autophagy is closely associated with apoptosis, and a pro-inflammatory and/or catabolic disc microenvironment could set in motion a vicious cycle that leads to IVD degeneration.

Advanced glycation end products. Produced by non-enzymatic reactions between reducing sugars and amino acid groups in proteins, lipids and nucleic acids, AGEs accumulate and cause tissue damage in patients with T2DM via irreversible changes to ECM components and blood vessel walls[43]. AGEs decrease the hydrophilic charge of ECM glycosaminoglycans, correlated with reduced disc hydration and endplate sclerosis (with endplate thickening and reduced porosity)[97]. AGE-induced changes in the CEP microarchitecture affect the biomechanical behaviour of the IVD; that is, they diminish IVD creep deformation and increase disc stiffness. Concomitantly, the interaction of AGEs with their receptors (RAGEs) is associated with increased production of ROS, expression of pro-inflammatory cytokines, as well as genes associated with hypoxia and catabolism, and decreased markers of ECM health (metalloproteinase inhibitor 1 and type II collagen)[97,101]. Moreover, the elasticity of IVD tissue is reduced by protein crosslinking with AGEs[43]. As chronic dietary intake of AGEs contributes to ageing-accelerated alterations to the IVD, including loss of glycosaminoglycans, increased vertebral cortical thickness and ectopic calcification of bony endplates, restricting intake AGE-rich foods might prevent IVD degeneration in patients with T2DM[109].

Adipokines. Supporting a strict correlation between adipokines, T2DM and the aetiology and development of IVD degeneration, in the LEP-R-deficient (db/db) mouse, a well-established model of T2DM, a diminished vertebral bone mass and increased risk of IVD failure were associated with altered mechanical properties, increased intradiscal notochordal band area and increased expression of MMP-13 and apoptosis in IVD[110,111]. Patients with T2DM have hyperleptinaemia and downregulation of adiponectin, which are restored by treatment with anti-diabetic drugs. In particular, sitagliptin, metformin, pioglitazone, liraglutide and empagliflozin reduce leptin levels[112], whereas the PPARγ agonists thiazolidinediones, such as pioglitazone and rosiglitazone, increase circulating concentrations of adiponectin in both animals and humans[113]. Mounting evidence from preclinical research correlates the pathological expansion of adipose tissue and the associated dysregulated adipokine production with an increase in the risk of developing T2DM mediated by modulation

Box 2 | **T2DM and IVD degeneration**

- Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, hyperglycaemia, hyperinsulinemia and accumulation of advanced glycation end products (AGEs). These alterations induce pathophysiological changes to the intervertebral disc (IVD) including decreased nutrient supply, decreased disc cell viability and extracellular matrix degradation.
- T2DM-associated hyperinsulinaemia induces an increase in bone mineral density, leading to endplate sclerosis.
- T2DM-associated increase in AGEs causes microvessel injury, limiting blood flow and nutrient supply to IVD cells as well as reducing the clearance of local inflammatory mediators and toxins.
- High glucose levels induce production of reactive oxygen species, mitochondrial stress and premature senescence in annulus fibrosus and nucleus pulposus cells.
- Hyperglycaemia increases apoptotic mechanisms, decreases autophagic mechanisms and contributes to an inflammatory catabolic microenvironment in IVD degeneration.

of the underlying pathophysiological mechanisms, including insulin resistance, vascular inflammation and endothelial dysfunction[114]. Nevertheless, the clinical implications of these associations, in particular their potential implications for diagnosis, prognosis and therapy, have not been fully established.

Leptin and adiponectin can modulate insulin sensitivity by reducing the production of glucose by the liver, increasing fatty acid oxidation and decreasing triglyceride levels in skeletal muscle[115]. Moreover, converging pathways of insulin and adipokine signalling are responsible for sensing insulin inputs in insulin-responsive tissues[113,115]. Because AdipoR1 and AdipoR2 activate insulin receptor substrate 1 (IRS-1), IRS-2, AMPK, PPARα and p38 MAPK, with concomitant translocation of the glucose transporter GLUT4, glucose uptake and fatty acid oxidation, adiponectin replacement therapy or dietary interventions that are aimed at restoring adiponectin secretion by adipose tissue have been suggested as therapeutic strategies for T2DM[113]. Glucose uptake is also increased by omentin and visfatin, which agonistically bind insulin receptor but not insulin-like growth factor 1 receptor, and insulin sensitivity is increased by vaspin, apelin and omentin[115] (TABLE 1). Activation of LEP-R induces inhibition of ATP-sensitive potassium channels, phosphodiesterase 3B activation, decrease in cAMP levels and inhibition of phospholipase C-protein c, overall leading to the inhibition of insulin secretion[115]. Ghrelin can modulate insulin receptor signalling as well as inhibit insulin secretion[115]. By contrast, resistin induces insulin resistance, suppresses insulin-stimulated glucose uptake and increases plasma concentrations of glucose, effects that are reversed by administration of anti-resistin antibody[115].

Vascular function is affected by T2DM-associated dysregulation of adipokine concentrations, thus increasing the risk of cardiovascular complications. Leptin, chemerin and resistin have deleterious vascular effects by causing vasoconstriction, promoting the proliferation and migration of smooth muscle cells or inducing expression of prothrombotic and pro-inflammatory factors as well as adhesion molecules[116]. Conversely, adiponectin and omentin have anti-inflammatory as well as endothelium-protective effects through the inhibition of smooth muscle cell proliferation and migration, enhancement of endothelial nitric oxide-mediated vasodilation or reduction in the expression of adhesion molecules and, thus, leukocyte–endothelium interactions, a critical step in the development of macrovascular and microvascular complications[116].

By governing T2DM-associated insulin resistance and vascular complications, adipokines are evidently critical contributors to T2DM progression, especially in the maintenance of hyperinsulinaemia, hyperglycaemia and microvessel injury, thus contributing to pathophysiological mechanisms associated with IVD degeneration.

Bacteria and TLRs in the IVD

TLRs initiate immune responses to bacterial pathogens and are thus crucial to the innate immune systems. TLRs are also activated by TLR ligands that originate from the degradation of host tissue. Emerging evidence suggests that bacterial TLR ligands and ECM degradation products mediate ligand-mediated TLR signalling in the process of IVD degeneration, in response to internal (host-derived) and external (pathogen-derived) signals. Research has shown that anaerobic bacteria are present in a large percentage of painful, herniated discs[117,118] and that discs infected with anaerobic bacteria are more likely to develop Modic changes in the adjacent vertebrae than sterile discs or those with aerobic infections[118]. These observations have led to the development of novel hypotheses about the importance of bacteria in the pathogenesis of LBP[119]. These new hypotheses are contributing to new research to determine whether low-grade bacterial infection, particularly with anaerobic bacteria, can contribute to IVD degeneration and LBP and whether antibiotics might be used to treat these conditions. Indeed, the first randomized controlled trial, published in 2013, showed that antibiotic intervention was more effective than placebo in patients with LBP and type 1 Modic changes[120]

A systematic review concluded that bacteria are common in the IVD of people undergoing spinal surgery[121]. The analysis found moderate evidence of an association between the presence of bacteria and LBP with disc herniation, and between bacterial infection and Modic changes with disc herniation, and there was modest evidence of a causal relationship between the presence of bacteria and LBP. Whether these microorganisms are found in IVDs as a result of actual infection or because of contamination remains a matter of debate[121]. Among the bacteria implicated in degenerative disc disease and the development of Modic changes are *Cutibacterium acnes*, which are bacteria commonly found in the skin, hair follicles and sebaceous glands[122]. This observation has led to suggestions that long-term treatment with antibiotics that are used for the treatment of acne could be used, albeit cautiously, to resolve symptoms associated with chronic LBP[122]. However, a 2019 randomized controlled trial by Norwegian researchers[123] could not replicate the results of the only previous randomized trial to assess the efficacy of antibiotic treatment in patients with LBP[120], as treatment with amoxicillin for 3 months did not produce clinically relevant benefits compared with placebo.

Anaerobic bacteria in the IVD might stimulate inflammatory pathways through TLRs to further exacerbate disc degeneration. However, it has also been proposed that the altered immunometabolism associated with T2DM and metabolic syndrome can lead to the formation of ECM degradation products that equally have the ability to engage TLRs and activate many of the same inflammatory pathways as seen during microbial infection[124]. This idea fits perfectly well with evidence emerging from research in OA, suggesting that TLRs are activated in both OA and IVD degeneration, linking mechanical stress, pro-inflammatory cytokines, IVD and cartilage degeneration to pain via increased neurotrophic, angiogenic and nociceptive factors[125–128]. Therefore, TLRs are important players in catabolic cell signalling in the context of IVD degeneration, but their activation need not necessarily occur through bacterial infections. Endogenous TLR ligands, including ECM degradation

products, are likely to mediate ligand-mediated TLR signalling in the process of IVD degeneration[129–131].

Conclusions

The classic literature on the physiology of the IVD has established that the acidic milieu of this structure leads to the development of a highly catabolic microenvironment, which has adverse effects on metabolism. Studies from the past 20 years suggest that fibrosis is a feature of IVD degeneration and fibrotic events could be linked to immunometabolic changes, especially in patients with insulin resistance and diabetes mellitus. Overweight also profoundly affects IVD degeneration. Therefore, the combination of declining oxygen and nutrient supply to the IVD and increasing levels of the pro-inflammatory adipokines reviewed herein alter the phenotype of IVD cells, negatively affecting their metabolic rate. Metabolism is known to be drastically altered in chondrocytes in OA, and aberrant immunometabolism of cells could be a key feature of ECM degradation in many phenotypes of OA[132]. Similar mechanisms may operate in IVD degeneration; the combined effects of pathological starvation and elevation of adipokines are likely to lead to immunometabolic alterations, and these must be studied in greater detail to identify new therapeutic targets that may benefit research on spine and cartilage. Emphasizing the similarities and substantial overlaps between OA and IVD degeneration, rather than their differences, will raise awareness of the many basic, translational and clinical research opportunities at the intersection of OA and IVD degeneration research. Collaboration between clinicians and scientists involved in both fields can provide cross-fertilization of research in order to improve treatments and diagnostics for both conditions[27]. At present, there are no drugs that specifically target immunometabolic alterations in OA and IVD degeneration. However, we know that implementing behavioural changes, increasing physical activity and avoiding obesity and diabesity are the only preventive measures for OA and IVD degeneration. Nonetheless, as far as we are aware, no clinical studies have been performed to assess the targeting of obesity and T2DM. Exploratory analysis of data from the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial suggests that inhibition of IL-1β with a biologic drug originally designed for the treatment of atherosclerosis and thrombosis benefited patients with OA, suggesting that this therapy could delay total knee replacement[133]. The findings of this analysis support further and more detailed investigation of IL-1β inhibition for the treatment of OA in large and load-bearing joints and of IVD degeneration in the spine. Biologic drugs that inhibit the function of the key adipokines involved in IVD degeneration should be trialled in clinical studies of LBP in the future.

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1. James, S. L. et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **392**, 1789–1858 (2018).
2. Jin, Z. et al. Incidence trend of five common musculoskeletal disorders from 1990 to 2017 at the global, regional and national level: results from the global burden of disease study 2017. *Ann. Rheum. Dis.* **79**, 1014–1022 (2020).
3. Ehrlich, G. E. Low back pain. *Bull. World Health Organ.* **81**, 671–676 (2003).
4. Hartvigsen, J. et al. What low back pain is and why we need to pay attention. *Lancet* **391**, 2356–2367 (2018).
5. Vlaeyen, J. W. S. et al. Low back pain. *Nat. Rev. Dis. Prim.* **4**, 52 (2018).
6. Cheung, K. M. C. et al. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. *Spine* **34**, 934–940 (2009).
7. Livshits, G. et al. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. *Ann. Rheum. Dis.* **70**, 1740–1745 (2011).
8. Takatalo, J. et al. Does lumbar disc degeneration on magnetic resonance imaging associate with low back symptom severity in young Finnish adults? *Spine* **36**, 2180–2189 (2011).
9. Brinjikji, W. et al. Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. *Am. J. Neuroradiol.* **36**, 811–816 (2015).
10. Gallucci, M., Puglielli, E., Splendiani, A., Pistoia, F. & Spacca, G. Degenerative disorders of the spine. *Eur. Radiol.* **15**, 591–598 (2005).
11. Kushchayev, S. V. et al. ABCs of the degenerative spine. *Insights Imaging* **9**, 253–274 (2018).
12. Buckwalter, J. A. Aging and degeneration of the human intervertebral disc. *Spine* **20**, 1307–1314 (1995).
13. Dudli, S. et al. ISSLS Prize in Basic Science 2017: intervertebral disc/bone marrow cross-talk with Modic changes. *Eur. Spine J.* **26**, 1362–1373 (2017).
14. Dudli, S., Fields, A. J., Samartzis, D., Karppinen, J. & Lotz, J. C. Pathobiology of Modic changes. *Eur. Spine J.* **25**, 3723–3734 (2016).
15. Anderson, D. G. & Tannoury, C. Molecular pathogenic factors in symptomatic disc degeneration. *Spine J.* **5**, S260–S266 (2005).
16. Silagi, E. S. et al. The role of HIF proteins in maintaining the metabolic health of the intervertebral disc. *Nat. Rev. Rheumatol.* **17**, 426–439 (2021).
17. Kadow, T., Sowa, G., Vo, N. & Kang, J. D. Molecular basis of intervertebral disc degeneration and herniations: what are the important translational questions? *Clin. Orthop. Relat. Res.* **473**, 1903–1912 (2015).
18. Rajasekaran, S. et al. Human intervertebral discs harbour a unique microbiome and dysbiosis determines health and disease. *Eur. Spine J.* **29**, 1621–1640 (2020).
19. Scanzello, C. R. Role of low-grade inflammation in osteoarthritis. *Curr. Opin. Rheumatol.* **29**, 79–85 (2017).
20. Robinson, W. H. et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nat. Rev. Rheumatol.* **12**, 580–592 (2016).
21. Berenbaum, F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis Cartilage* **21**, 16–21 (2013).
22. Courties, A., Sellam, J. & Berenbaum, F. Metabolic syndrome-associated osteoarthritis. *Curr. Opin. Rheumatol.* **29**, 214–222 (2017).
23. Courties, A. & Sellam, J. Osteoarthritis and type 2 diabetes mellitus: what are the links? *Diabetes Res. Clin. Pract.* **122**, 198–206 (2016).
24. Francisco, V. et al. Adipokines: linking metabolic syndrome, the immune system, and arthritic diseases. *Biochem. Pharmacol.* **165**, 196–206 (2019).
25. Sharma, A. The role of adipokines in intervertebral disc degeneration. *Med. Sci.* **6**, 34 (2018).
26. Ruiz-Fernández, C. et al. Molecular relationships among obesity, inflammation and intervertebral disc degeneration: are adipokines the common link? *Int. J. Mol. Sci.* **20**, 2030 (2019).
27. Rustenburg, C. M. E. et al. Osteoarthritis and intervertebral disc degeneration: quite different, quite similar. *JOR Spine* **1**, e1033 (2018).
28. Czech, M. P. Insulin action and resistance in obesity and type 2 diabetes. *Nat. Med.* **11**, 804–814 (2017).
29. Astrup, A. & Finer, N. Redefining type 2 diabetes: "diabesity" or "obesity dependent diabetes mellitus"? *Obes. Rev.* **1**, 57–59 (2000).
30. Toplak, H. et al. "Diabesity" — obesity and type 2 diabetes (Update 2019). *Wien. Klin. Wochenschr.* **131**, 71–76 (2019).
31. Aamir, K., Khan, H. U., Sethi, G., Hossain, M. A. & Arya, A. Wnt signaling mediates TLR pathway and promote unrestrained adipogenesis and metaflammation: therapeutic targets for obesity and type 2 diabetes. *Pharmacol. Res.* **152**, 104602 (2020).
32. Samartzis, D., Karppinen, J., Chan, D., Luk, K. D. K. & Cheung, K. M. C. The association of lumbar intervertebral disc degeneration on magnetic resonance imaging with body mass index in overweight and obese adults: a population-based study. *Arthritis Rheum.* **64**, 1488–1496 (2012).
33. Elgaeva, E. E. et al. ISSLS Prize in Clinical Science 2020. Examining causal effects of body mass index on back pain: a Mendelian randomization study. *Eur. Spine J.* **29**, 686–691 (2020).
34. Grunhagen, T., Shirazi-Adl, A., Fairbank, J. C. T. & Urban, J. P. G. Intervertebral disk nutrition: a review of factors influencing concentrations of nutrients and metabolites. *Orthop. Clin. North. Am.* **42**, 465–477 (2011).
35. Shi, J. et al. Increased lactic acid content associated with extracellular matrix depletion in a porcine disc degeneration induced by superficial annular lesion. *BMC Musculoskelet. Disord.* **20**, 551 (2019).
36. Guehring, T. et al. Notochordal intervertebral disc cells: sensitivity to nutrient deprivation. *Arthritis Rheum.* **60**, 1026–1034 (2009).
37. Zhao, Y. et al. Body mass index and polycystic ovary syndrome: a 2-sample bidirectional mendelian randomization study. *J. Clin. Endocrinol. Metab.* **105**, dgaa125 (2020).
38. Urban, J. P. G. & Roberts, S. Degeneration of the intervertebral disc. *Arthritis Res. Ther.* **5**, 120–130 (2003).
39. Yin, X. et al. Effects of glucose deprivation on ATP and proteoglycan production of intervertebral disc cells under hypoxia. *Sci. Rep.* **10**, 8899 (2020).
40. Wills, C. R., Foata, B., González Ballester, M., Karppinen, J. & Noailly, J. Theoretical explorations generate new hypotheses about the role of the cartilage endplate in early intervertebral disk degeneration. *Front. Physiol.* **9**, 1210 (2018).

41. Rade, M. et al. Vertebral endplate defect as initiating factor in intervertebral disc degeneration. *Spine* **43**, 412–419 (2018).
42. Määttä, J. H. et al. Strong association between vertebral endplate defect and Modic change in the general population. *Sci. Rep.* **8**, 16630 (2018).
43. Alpantaki, K., Kampouroglou, A., Koutserimpas, C., Effraimidis, G. & Hadjipavlou, A. Diabetes mellitus as a risk factor for intervertebral disc degeneration: a critical review. *Eur. Spine J.* **28**, 2129–2144 (2019).
44. Cannata, F. et al. Osteoarthritis and type 2 diabetes: from pathogenetic factors to therapeutic intervention. *Diabetes Metab. Res. Rev.* **36**, e3254 (2020).
45. Takatalo, J. et al. Association of abdominal obesity with lumbar disc degeneration — a magnetic resonance imaging study. *PLoS One* **8**, e56244 (2013).
46. Lee, S. Y., Kim, W., Lee, S. U. & Choi, K. H. Relationship between obesity and lumbar spine degeneration: a cross-sectional study from the Fifth Korean National Health and Nutrition Examination Survey, 2010-2012. *Metab. Syndr. Relat. Disord.* **17**, 60–66 (2019).
47. Xu, X., Li, X. & Wu, W. Association between overweight or obesity and lumbar disk diseases a meta-analysis. *J. Spinal Disord. Tech.* **28**, 370–376 (2015).
48. Liuke, M. et al. Disc degeneration of the lumbar spine in relation to overweight. *Int. J. Obes.* **29**, 903–908 (2005).
49. Chen, J. et al. Fat mass and obesity-associated (FTO) gene polymorphisms are associated with risk of intervertebral disc degeneration in Chinese Han population: a case control study. *Med. Sci. Monit.* **24**, 5598–5609 (2018).
50. Wu, Z., Yang, Y. & Qiu, G. Association study between the polymorphisms of the fat mass- and obesity-associated gene with the risk of intervertebral disc degeneration in the Han Chinese population. *Genet. Test. Mol. Biomark.* **17**, 756–762 (2013).
51. Dario, A. B. et al. The relationship between obesity, low back pain, and lumbar disc degeneration when genetics and the environment are considered: a systematic review of twin studies. *Spine J.* **15**, 1106–1117 (2015).
52. Okada, E. et al. Aging of the cervical spine in healthy volunteers: a 10-year longitudinal magnetic resonance imaging study. *Spine* **34**, 706–712 (2009).
53. Francisco, V. et al. Obesity, fat mass and immune system: role for leptin. *Front. Physiol.* **9**, 640 (2018).
54. Scheja, L. & Heeren, J. The endocrine function of adipose tissues in health and cardiometabolic disease. *Nat. Rev. Endocrinol.* **15**, 507–524 (2019).
55. Gruber, H. E., Ingram, J. A., Hoelscher, G. L. & Hanley, E. N. Leptin expression by annulus cells in the human intervertebral disc. *Spine J.* **7**, 437–443 (2007).
56. Zhao, C. Q., Liu, D., Li, H., Jiang, L. S. & Dai, L. Y. Expression of leptin and its functional receptor on disc cells: contribution to cell proliferation. *Spine* **33**, 858–864 (2008).
57. Li, Z. et al. Leptin induces cyclin d1 expression and proliferation of human nucleus pulposus cells via JAK/STAT, PI3K/Akt and MEK/ERK Pathways. *PLoS One* **7**, e53176 (2012).
58. Koerner, J. D. et al. Differential gene expression in anterior and posterior annulus fibrosus. *Spine* **39**, 1917–1923 (2014).
59. Li, Z. et al. The role of leptin on the organization and expression of cytoskeleton elements in nucleus pulposus cells. *J. Orthop. Res.* **31**, 847–857 (2013).
60. Li, Z. et al. Leptin activates RhoA/ROCK pathway to induce cytoskeleton remodeling in nucleus pulposus cells. *Int. J. Mol. Sci.* **15**, 1176–1188 (2014).
61. Segar, A. H., Fairbank, J. C. T. & Urban, J. Leptin and the intervertebral disc: a biochemical link exists between obesity, intervertebral disc degeneration and low back pain — an in vitro study in a bovine model. *Eur. Spine J.* **28**, 214–223 (2019).
62. Miao, D. & Zhang, L. Leptin modulates the expression of catabolic genes in rat nucleus pulposus cells through the mitogen-activated protein kinase and Janus kinase 2/signal transducer and activator of transcription 3 pathways. *Mol. Med. Rep.* **12**, 1761–1768 (2015).
63. Li, Z. et al. Leptin downregulates aggrecan through the p38-ADAMST pathway in human nucleus pulposus cells. *PLoS One* **9**, e109595 (2014).
64. Han, Y. C. et al. Leptin regulates disc cartilage endplate degeneration and ossification through activation of the MAPK-ERK signalling pathway in vivo and in vitro. *J. Cell. Mol. Med.* **22**, 2098–2109 (2018).
65. Ding, W. et al. Leptin induces terminal differentiation of rat annulus fibrosus cells via activation of MAPK signaling. *Anat. Rec.* **296**, 1806–1812 (2013).
66. Sun, C., Wang, Z., Tian, J.-W. & Wang, Y.-H. Leptin-induced inflammation by activating IL-6 expression contributes to the fibrosis and hypertrophy of ligamentum flavum in lumbar spinal canal stenosis. *Biosci. Rep.* **38**, 20171214 (2018).
67. Liu, M. & Liu, F. Regulation of adiponectin multimerization, signaling and function. *Best. Pract. Res. Clin. Endocrinol. Metab.* **28**, 25–31 (2014).
68. Yuan, X. et al. The key role of canonical Wnt/β-catenin signaling in cartilage chondrocytes. *Curr. Drug Targets* **17**, 475–484 (2015).
69. Rodríguez-Carrio, J. et al. Non-esterified fatty acids profiling in rheumatoid arthritis: associations with clinical features and Th1 response. *PLoS One* **11**, e0159573 (2016).
70. Khabour, O. F., Abu-Rumeh, L., Al-Jarrah, M., Jamous, M. & Alhashimi, F. Association of adiponectin protein and ADIPOQ gene variants with lumbar disc degeneration. *Exp. Ther. Med.* **8**, 1340–1344 (2014).
71. Yuan, B. et al. Adiponectin downregulates TNF-α expression in degenerated intervertebral discs. *Spine* **43**, E381–E389 (2018).
72. Terashima, Y. et al. Expression of adiponectin receptors in human and rat intervertebral disc cells and changes in receptor expression during disc degeneration using a rat tail temporary static compression model. *J. Orthop. Surg. Res.* **11**, 1–9 (2016).
73. Steppan, C. M. et al. The hormone resistin links obesity to diabetes. *Nature* **409**, 307–312 (2001).
74. Tarkowski, A., Bjersing, J., Shestakov, A. & Bokarewa, M. I. Resistin competes with lipopolysaccharide for binding to toll-like receptor 4. *J. Cell. Mol. Med.* **14**, 1419–1431 (2010).
75. Francisco, V. et al. Biomechanics, obesity, and osteoarthritis. The role of adipokines: when the levee breaks. *J. Orthop. Res.* **36**, 594–604 (2017).
76. Li, Z. et al. Resistin promotes CCL4 expression through toll-like receptor-4 and activation of the p38-MAPK and NF-κB signaling pathways: implications for intervertebral disc degeneration. *Osteoarthritis Cartilage* **25**, 341–350 (2017).
77. Liu, C. et al. Resistin promotes intervertebral disc degeneration by upregulation of ADAMTS-5 through p38 MAPK signaling pathway. *Spine* **41**, 1414–1420 (2016).
78. Shi, C. et al. Nicotinamide phosphoribosyltransferase inhibitor APO866 prevents IL-1β-induced human nucleus pulposus cell degeneration via autophagy. *Cell. Physiol. Biochem.* **49**, 2463–2482 (2018).
79. Abella, V. et al. The potential of lipocalin-2/NGAL as biomarker for inflammatory and metabolic diseases. *Biomarkers* **20**, 565–571 (2015).
80. Kao, T.-H. et al. Nerve growth factor increases MMP9 activity in annulus fibrosus cells by upregulating lipocalin 2 expression. *Eur. Spine J.* **24**, 1959–1968 (2015).
81. Kao, T.-H., Peng, Y.-J., Tsou, H.-K., Salter, D. M. & Lee, H.-S. Nerve growth factor promotes expression of novel genes in intervertebral disc cells that regulate tissue degradation. *J. Neurosurg. Spine* **21**, 653–661 (2014).
82. Francisco, V. et al. Adipokines and inflammation: is it a question of weight? *Br. J. Pharmacol.* **175**, 1569–1579 (2018).
83. Liu, C. J. & Bosch, X. Progranulin: a growth factor, a novel TNFR ligand and a drug target. *Pharmacol. Ther.* **133**, 124–132 (2012).
84. Wang, S. et al. Progranulin is positively associated with intervertebral disc degeneration by interaction with IL-10 and IL-17 through TNF pathways. *Inflammation* **41**, 1852–1863 (2018).
85. Naphade, S. B. et al. Progranulin expression is upregulated after spinal contusion in mice. *Acta Neuropathol.* **119**, 123–133 (2010).
86. Zhao, Y.-P. et al. Progranulin knockout accelerates intervertebral disc degeneration in aging mice. *Sci. Rep.* **5**, 9102 (2015).
87. Ding, H. et al. Progranulin derived engineered protein Atsttrin suppresses TNF-a-mediated inflammation in intervertebral disc degenerative disease. *Oncotarget* **8**, 109692–109702 (2017).
88. Lorenzi, T. et al. Ghrelin: a metabolic signal affecting the reproductive system. *Cytokine Growth Factor. Rev.* **20**, 137–152 (2009).
89. Colldén, G., Tschöp, M. H. & Müller, T. D. Therapeutic potential of targeting the ghrelin pathway. *Int. J. Mol. Sci.* **18**, 798 (2017).
90. Pereira, J. A. D. S., Silva, F. C. D. & De Moraes-Vieira, P. M. M. The impact of ghrelin in metabolic diseases: an immune perspective. *J. Diabetes Res.* **2017**, 4527980 (2017).
91. Li, W. et al. Ghrelin protects against nucleus pulposus degeneration through inhibition of NF-κB signaling pathway and activation of Akt signaling pathway. *Oncotarget* **8**, 91887–91901 (2017).
92. Teraguchi, M. et al. Progression, incidence, and risk factors for intervertebral disc degeneration in a longitudinal population-based cohort: the Wakayama Spine Study. *Osteoarthritis Cartilage* **25**, 1122–1131 (2017).
93. Liu, X., Pan, F., Ba, Z., Wang, S. & Wu, D. The potential effect of type 2 diabetes mellitus on lumbar disc degeneration: a retrospective single-center study. *J. Orthop. Surg. Res.* **13**, 52 (2018).
94. Fabiane, S. M., Ward, K. J., Iatridis, J. C. & Williams, F. M. K. Does type 2 diabetes mellitus promote intervertebral disc degeneration? *Eur. Spine J.* **25**, 2716–2720 (2016).
95. Hangai, M. et al. Factors associated with lumbar intervertebral disc degeneration in the elderly. *Spine J.* **8**, 732–740 (2008).
96. Videman, T. et al. Disc degeneration and bone density in monozygotic twins discordant for insulin-dependent diabetes mellitus. *J. Orthop. Res.* **18**, 768–772 (2000).
97. Fields, A. J. et al. Alterations in intervertebral disc composition, matrix homeostasis and biomechanical behavior in the UCD-T2DM rat model of type 2 diabetes. *J. Orthop. Res.* **33**, 738–746 (2015).
98. Huang, Y. C., Urban, J. P. G. & Luk, K. D. K. Intervertebral disc regeneration: do nutrients lead the way? *Nat. Rev. Rheumatol.* **10**, 561–566 (2014).
99. Thrailkill, K. M. Is insulin an anabolic agent in bone? Dissecting the diabetic bone for clues. *Am. J. Physiol. Endocrinol. Metab.* **289**, E735–E745 (2005).
100. Xu, H. M., Hu, F., Wang, X. Y. & Tong, S. L. Relationship between apoptosis of endplate microvasculature and degeneration of the intervertebral disk. *World Neurosurg.* **125**, e392–e397 (2019).
101. Chen, S., Liao, M., Li, J., Peng, H. & Xiong, M. The correlation between microvessel pathological changes of the endplate and degeneration of the intervertebral disc in diabetic rats. *Exp. Ther. Med.* **5**, 711–717 (2013).
102. Jiang, L. et al. Apoptosis, senescence, and autophagy in rat nucleus pulposus cells: implications for diabetic intervertebral disc degeneration. *J. Orthop. Res.* **31**, 692–702 (2013).
103. Liu, Y. et al. The effect of high glucose on the biological characteristics of nucleus pulposus-derived mesenchymal stem cells. *Cell Biochem. Funct.* **38**, 130–140 (2020).
104. Jiang, Z. et al. High glucose-induced excessive reactive oxygen species promote apoptosis through mitochondrial damage in rat cartilage endplate cells. *J. Orthop. Res.* **36**, 2476–2483 (2018).
105. Hou, G. et al. N-cadherin attenuates high glucose-induced nucleus pulposus cell senescence through regulation of the ROS/NF-κB pathway. *Cell. Physiol. Biochem.* **47**, 257–265 (2018).
106. Kong, J. G., Park, J. B., Lee, D. & Park, E. Y. Effect of high glucose on stress-induced senescence of nucleus pulposus cells of adult rats. *Asian Spine J.* **9**, 155–161 (2015).
107. Park, J.-B., Kong, J.-G., Lee, D. & Park, E.-Y. Stressed-induced senescence of adult rat nucleus pulposus cells effect of high glucose on stress-induced senescence of nucleus pulposus cells of adult rats. *Asian Spine J.* **9**, 155–161 (2015).
108. Cheng, X., Ni, B., Zhang, F., Hu, Y. & Zhao, J. High glucose-induced oxidative stress mediates apoptosis and extracellular matrix metabolic imbalances possibly via p38 MAPK activation in rat nucleus pulposus cells. *J. Diabetes Res.* **2016**, 3765173 (2016).
109. Svenja, I. J. et al. Chronic ingestion of advanced glycation end products induces degenerative spinal changes and hypertrophy in aging pre-diabetic mice. *PLoS One* **10**, e0116625 (2015).
110. Li, X. et al. Intervertebral disc degeneration in mice with type II diabetes induced by leptin receptor deficiency. *BMC Musculoskelet. Disord.* **21**, 77 (2020).
111. Natelson, D. M. et al. Leptin signaling and the intervertebral disc: sex dependent effects of leptin receptor deficiency and Western diet on the spine in a type 2 diabetes mouse model. *PLoS One* **15**, e0227527 (2020).

112. Katsiki, N., Mikhailidis, D. P. & Banach, M. Leptin, cardiovascular diseases and type 2 diabetes mellitus. *Acta Pharmacol. Sin.* **39**, 1176–1188 (2018).
113. Achari, A. E. & Jain, S. K. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int. J. Mol. Sci.* **18**, 1321 (2017).
114. Eckel, R. H. et al. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? *J. Clin. Endocrinol. Metab.* **96**, 1654–1663 (2011).
115. Jaganathan, R., Ravindran, R. & Dhanasekaran, S. Emerging role of adipocytokines in Type 2 diabetes as mediators of insulin resistance and cardiovascular disease. *Can. J. Diabetes* **42**, 446–456.e1 (2018).
116. El Husseny, M. W. A. et al. Adipokines: potential therapeutic targets for vascular dysfunction in type II diabetes mellitus and obesity. *J. Diabetes Res.* **2017**, 8095926 (2017).
117. Tang, G. et al. Latent infection of low-virulence anaerobic bacteria in degenerated lumbar intervertebral discs. *BMC Musculoskelet. Disord.* **19**, 445 (2018).
118. Albert, H. B. et al. Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur. Spine J.* **22**, 690–696 (2013).
119. Fisher, T. J. & Osti, O. L. Do bacteria play an important role in the pathogenesis of low back pain? *ANZ J. Surg.* **85**, 808–814 (2015).
120. Albert, H. B. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. *Eur. Spine J.* **22**, 697–707 (2013).
121. Urquhart, D. M. et al. Could low grade bacterial infection contribute to low back pain? A systematic review. *BMC Med.* **13**, 13 (2015).
122. Khalil, J. G., Gandhi, S. D., Park, D. K. & Fischgrund, J. S. Cutibacterium acnes in spine pathology: pathophysiology, diagnosis, and management. *J. Am. Acad. Orthop. Surg.* **27**, e633–e640 (2019).
123. Bråten, L. C. H. et al. Efficacy of antibiotic treatment in patients with chronic low back pain and Modic changes (the AIM study): double blind, randomised, placebo controlled, multicentre trial. *BMJ* **367**, l5654 (2019).
124. Gorth, D. J., Shapiro, I. M. & Risbud, M. V. Discovery of the drivers of inflammation induced chronic low back pain: from bacteria to diabetes. *Discov. Med.* **20**, 177–184 (2015).
125. MV, R. & IM, S. Role of cytokines in intervertebral disc degeneration: pain and disc content. *Nat. Rev. Rheumatol.* **10**, 44–56 (2014).
126. Krock, E. et al. Painful, degenerating intervertebral discs up-regulate neurite sprouting and CGRP through nociceptive factors. *J. Cell. Mol. Med.* **18**, 1213–1225 (2014).
127. Alkhatib, B. et al. Acute mechanical injury of the human intervertebral disc: link to degeneration and pain. *Eur. Cell Mater.* **28**, 98–111 (2014).
128. Binch, A. L. et al. Expression and regulation of neurotrophic and angiogenic factors during human intervertebral disc degeneration. *Arthritis Res. Ther.* **16**, 416 (2014).
129. Gómez, R., Villalvilla, A., Largo, R., Gualillo, O. & Herrero-Beaumont, G. TLR4 signalling in osteoarthritis-finding targets for candidate DMOADs. *Nat. Rev. Rheumatol.* **11**, 159–170 (2015).
130. Yu, L., Wang, L. & Chen, S. Endogenous toll-like receptor ligands and their biological significance. *J. Cell. Mol. Med.* **14**, 2592–2603 (2010).
131. Kawasaki, T. & Kawai, T. Toll-like receptor signaling pathways. *Front. Immunol.* **5**, 461 (2014).
132. Mobasheri, A. et al. The role of metabolism in the pathogenesis of osteoarthritis. *Nat. Rev. Rheumatol.* **13**, 302–311 (2017).
133. Schieker, M. et al. Effects of interleukin-1β inhibition on incident hip and knee replacement: exploratory analyses from a randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* **173**, 509–515 (2020).
134. Tarkowski, A., Bokarewa, M., Nagaev, I., Dahlberg, L. & Smith, U. Proinflammatory properties resistin, an adipokine with potent. *J. Immunol. Ref.* **174**, 5789–5795 (2005).
135. Franco-Trepat, E. et al. Visfatin connection: present and future in osteoarthritis and osteoporosis. *J. Clin. Med.* **8**, 1178 (2019).
136. Wei, J., Hettinghouse, A. & Liu, C. The role of progranulin in arthritis. *Ann. N. Y. Acad. Sci.* **1383**, 5–20 (2016).
137. Otero, M. et al. Chronic inflammation modulates ghrelin levels in humans and rats. *Rheumatology* **43**, 306–310 (2004).
138. Francisco, V. et al. Levels of the novel endogenous antagonist of ghrelin receptor, liver-enriched antimicrobial peptide-2, in patients with rheumatoid arthritis. *Nutrients* **12**, 1006 (2020).
139. Gerwick, L., Corley-Smith, G. & Bayne, C. J. Gene transcript changes in individual rainbow trout livers following an inflammatory stimulus. *Fish. Shellfish. Immunol.* **22**, 157–171 (2007).
140. Escoté, X. et al. Role of omentin, vaspin, cardiotrophin-1, TWEAK and NOV/CCN3 in obesity and diabetes development. *Int. J. Mol. Sci.* **18**, 1770 (2017).
141. Kuba, K., Sato, T., Imai, Y. & Yamaguchi, T. Apelin and Elabela/Toddler; double ligands for APJ/Apelin receptor in heart development, physiology, and pathology. *Peptides* **111**, 62–70 (2019).
142. Helfer, G. & Wu, Q. F. Chemerin: a multifaceted adipokine involved in metabolic disorders. *J. Endocrinol.* **238**, R79–R94 (2018).
143. Sakai, D. & Andersson, G. B. J. Stem cell therapy for intervertebral disc regeneration: obstacles and solutions. *Nat. Rev. Rheumatol.* **11**, 243–256 (2015).

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