White Rose Research Online

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk
Universities of Leeds, Sheffield and York

Deposited via The University of Leeds.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/104411/

Version: Accepted Version

Article:

Martell-Pelletier, J, Barr, AJ, Cicuttini, FM et al. (2016) Osteoarthritis. Nature Reviews Disease Primers, 2. 16072. ISSN: 2056-676X

https://doi.org/10.1038/nrdp.2016.72

© 2016 Macmillan Publishers Limited, part of Springer Nature. All rights reserved. This is an author produced version of a paper published in Nature Reviews Disease Primers. Uploaded in accordance with the publisher's self-archiving policy.

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

UNIVERSITY OF LEEDS
University of Sheffield
UNIVERSITY of York

OSTEOARTHRITIS

Johanne Martel-Pelletier[1], Andrew J. Barr[2], Flavia M. Cicuttini[3], Philip G. Conaghan[2], Cyrus Cooper[4], Mary B. Goldring[5], Steven R. Goldring[6], Graeme Jones[7], Andrew J. Teichtahl[3,8], Jean-Pierre Pelletier[1]

[1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, Quebec, Canada
[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK
[3]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, Australia
[4]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK and NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK
[5]The Hospital for Special Surgery and Department of Cell and Developmental Biology, Weill Cornell Medical College, New York, New York, USA
[6]The Hospital for Special Surgery, Research Division, and Department of Medicine, Weill Cornell Medical College, New York, New York, USA
[7]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia
[8]IDI Heart and Diabetes Institute, Melbourne, Australia

Correspondence to:

Jean-Pierre Pelletier, MD
email: dr@jppelletier.ca
Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM),
900 rue Saint-Denis, Suite R11.412, Montreal, Quebec, Canada H2X 0A9

Johanne Martel-Pelletier, PhD
email: jm@martelpelletier.ca
Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM),
900 rue Saint-Denis, Suite R11.412, Montreal, Quebec, Canada H2X 0A9

ABSTRACT

From prehistoric times to the present day, osteoarthritis (OA) has proven to be a most challenging disease. Indeed, this disease is the most common joint disorder, affecting mainly the diarthrodial joints, and is associated with an alarmingly increasing socioeconomic impact. Primary OA results from a combination of risk factors, with aging and obesity being the most prominent. The pathology of OA is still evolving, from being viewed as cartilage-limited to a multifactorial disease affecting the whole joint. Moreover, an intricate relationship between local and systemic factors modulates its clinical and structural presentations, leading to a common final pathway of articular destruction. Pharmacological treatments are mostly related to relief of symptoms and there is no disease-modifying OA drug (DMOAD) yet approved by the regulatory agencies. Identifying phenotypes of patients will enable detection of the disease in its early stages as well as distinguish individuals at higher risk of progression, which in turn could be used to guide clinical decision-making and allow more effective and specific therapeutic interventions to be designed. This primer is an update on the progress made in the field of OA epidemiology, quality of life, pathophysiological mechanisms, diagnosis, screening, prevention, and disease management.

[H1] INTRODUCTION

Not many diseases can claim to have a history as rich and ancient as osteoarthritis (OA). It can be traced back in time from paleopathological findings in skeletal remains[1,2] and historical depictions[3-6] and is suggested to be impervious to evolution[7]. Clinicians did not recognise OA until the late 18th century[8] and further nomenclature confusion delayed its recognition, as it was considered the same entity as rheumatoid arthritis[9].

To date, OA has proven to be a most challenging disease to treat, despite it being the most common degenerative joint disorder[10]. Even though it is among the oldest diseases affecting humankind, its definitions, risk factors and pathophysiology are still evolving. Cardinal signs include pain, transient morning stiffness, and crepitus on motion leading to instability and physical disability, thus impairing quality of life. The description of primary OA was long centred on the primacy of changes in the articular cartilage. The concept has evolved and OA is now considered a disease of the whole joint, and referred to as an "organ" disease. Primary OA results from a combination of risk factors, with aging and obesity being the most prominent. Other risk factors include knee malalignment, increased biomechanical loading of joints and bone density, genetics, and recently suggested low-grade systemic inflammation[11]. With regard to genetic factors, although there is strong evidence that they play an important role in radiographic OA of the hand and the spine[12,13], evidence is inconsistent for knee OA[14]. A recent meta-analysis showed that not one out of 199 published candidate OA genes has a significant association with knee OA and only two are associated with hip OA[15]. Regarding knee OA, one gene, the GDF5, was not included in the mentioned meta-analysis[15], but has already been confirmed as an OA susceptibility locus[16]. OA can be difficult to define as its development is often insidious, and clinically it represents a heterogeneous group of disorders involving different phenotypes with varying roots.

With the rapidly aging global population, it seems most appropriate at this time to review and highlight the progress made over the last several decades in the field of OA. The key advances in OA epidemiology, quality of life, pathophysiological mechanisms, diagnosis, screening and prevention, and disease management, as well as an update on the progress made are the focus of this primer.

[H1] EPIDEMIOLOGY

OA is a disorder of diverse aetiologies, which affects both large and small joints either singly or in combination. It is defined[17] as "a group of overlapping distinct entities with similar biologic, morphologic and clinical outcomes. The disease process affects all the tissues of the diarthrodial joint including the articular cartilage, subchondral bone, ligaments, capsule and synovial membrane, ultimately leading to joint failure." Although the disorder was previously classified as idiopathic (or primary) and secondary (based on the attribution of OA to recognised causative factors), a more helpful approach to understanding the epidemiology, risk factors and burden of OA is achieved through consideration of its impact on symptoms, structure and function[10,17]. Thus, joint pain is not a uniform accompaniment to structural change (such as joint space narrowing, osteophyte formation or subchondral sclerosis) and both pain and structural abnormality show variable relationships with physical function (ability to walk and undertake the activities of daily living). Symptomatic OA manifests principally with joint pain; structural change is visualised using plain radiography[18] or magnetic resonance imaging (MRI)[19]. Measurements of pain and structure need to be supplemented by indices of activity limitation and participation restriction. Standardised questionnaires are available for this purpose and they may be targeted at generic impairments such as general health, vitality and mental health (for example, the physical function scale of the SF-36 questionnaire) or disease-specific tools. The most widely used disease-specific questionnaires are those developed by the Western Ontario and McMaster Universities (WOMAC)[20], or those developed for the hip and knee by the Institute of Sports Sciences and Clinical Biomechanics: HOOS (Hip Disability and Osteoarthritis Outcome Score)[21] and KOOS (Knee Disability and Osteoarthritis Outcome Score)[22]. These obtain self-report information on impairments such as pain, stiffness and quality of life; activity limitations such as activities of daily living, sports participation and recreational activities; and participation restriction as part of general quality of life assessment.

[H2] Prevalence and incidence of OA

Prevalence and incidence estimates for OA differ widely, through variation in case definition and joint site under consideration[10,23]. Radiographic assessments (using scales such as those derived by Kellgren and Lawrence[24] over five decades ago, evaluating the severity of osteophyte formation, joint space narrowing, subchondral sclerosis, cyst formation and loss of joint congruity) provide the most widely available prevalence estimates for structural OA; this is reported in the hands of around 60% of adults aged 65 years and over, with comparable estimates for radiographic knee and hip OA from North American and European studies of 33% and 5% respectively[25,26]. Radiographic OA is more frequent among women than men at any given age over 50 years, with the gender difference most pronounced for hand and knee disease (**Figure 1**). Prevalence rates also rise steeply with age, in both genders. The frequency of pain at joint sites affected by OA is also variable: among men and women with structural hand OA, pain is only present in around 15% of cases, while this increases to around 50% of patients with radiographic knee OA and an even greater proportion of those with hip OA[23]. Conversely, the population frequency of knee pain is high (around 25%); among those with pain, radiographic changes are present in around 50% (12.5% overall), with associated disability in half of these (6% overall).

Individuals who develop symptomatic OA in one joint are more likely to have multiple joints involved, and this diathesis manifests clinically as a condition known as generalised OA[27]. This typically involves the joints of the hand (distal interphalangeal (DIP), proximal interphalangeal (PIP), thumb-base) as well as the cervico-lumbar spine, hips and knees. This variant is most frequent among older women and may be inherited in a polygenic pattern.

Although OA is worldwide in its distribution, geographic and ethnic differences in prevalence are apparent. European and American data does not differ markedly for hand and knee disease; however, hand involvement is particularly less frequent among native and African American populations, while the prevalence of knee and hip disease do not seem to vary to as great an extent[10,28]. In contrast, South Asian and Oriental populations appear to have a lower frequency of hip OA attributable in part to alterations in pelvic morphology[10].

Incidence studies of OA[29-31] also suggest high rates for symptomatic involvement of the hand, knee and hip in European and North American populations (**Figure 2**). A recent study from Spain[30] reported these as 6.5 (knee), 2.1 (hip) and 2.4 (hand) per 1000 person-years.

[H2] Risk factors for OA

The risk factors for OA can be divided into those that act at the level of individual susceptibility, and those that alter the biomechanical stability of individual joints[31,32]. Person-level risk factors include increasing age, female gender, joint biomechanics, genetic factors, inflammation and adiposity; the predominant joint-level factors are joint injury, repetitive joint use through occupation or leisure, and malalignment. Disease evolution in OA is slow, usually taking many years. Once established, the condition can remain relatively stable, clinically and radiologically, for several years. The distinct difference in definition between initiation and progression of disease remains controversial and it is difficult to estimate the extent to which risk factors for incidence and progression might differ. Index event bias complicates the search for true risk factors for progression[33], and progression risk is specific to the definition of OA utilised (structural or symptomatic) as well as the population studied. Some studies[31] have delineated comparable rates for each component of natural history (incidence 2.5%/yr; progression 3.6%/yr) and have suggested that certain risk factors selectively influence progression (obesity, malalignment, polyarticular diathesis, joint injury, crystal deposition, and high-impact physical activity)[33,34]. Among the 50% of individuals with radiographic OA who have frequent joint symptoms, MRI features that distinguished those with knee symptoms from those without, included bone marrow oedema lesions, meniscal lesions (which do not select for knee pain), synovial hypertrophy and effusion.

[H1] MECHANISMS/PATHOPHYSIOLOGY

This section focuses on the pathophysiology of OA in diarthrodial joints, e.g., the knee, hip or digits, which are the most common sites of OA. These joints join two adjacent bones, which are covered by a layer of specialised articular cartilage, and are encased in a connective tissue capsule lined by a synovial membrane, consisting of a thin cell layer of macrophages and fibroblasts[35]. The articular cartilage and underlying bone are separated by a layer of calcified cartilage (**Figure 3**) and the three tissues form a biocomposite, which is uniquely adapted to transfer loads during weight bearing and joint motion. Alteration in the integrity of the individual joint tissues can occur, acutely associated with traumatic injury, or can evolve over time through cell-mediated processes that alter the composition, structure and material properties of the joint tissues (**Table 1**). Although pathological processes may target a single tissue, because of their intimate physical and functional association, ultimately all of the joint tissues are affected and, in this sense, as mentioned earlier, OA is considered a whole joint disease. Following is a review of the normal structure and cellular physiology of articular cartilage, bone, and synovium and the current state of understanding of the interactions among these tissues in the physiological state and during the evolution of OA.

[H2] Cartilage

The articular cartilage is composed of more than 70% water, two major organic components, type II collagen and aggrecan, and a number of other collagens, proteoglycans, and non-collagenous proteins (**Figure 3**)[36-38]. The collagen network provides tensile strength and the charged proteoglycans provide compressive resilience by entrapping large quantities of water through their hydrophilic glycosaminoglycan (GAG) side chains[39,40]. The cartilage matrix is avascular and aneural and is populated by a single cell type, the chondrocyte. Under physiological conditions, the chondrocyte exhibits no mitotic activity and maintains minimal collagen turnover, since the half-life of type II collagen is more than 100 years. Because the proteoglycans have half-lives of weeks to years, the chondrocyte is involved mostly in replacing the GAG constituents on the aggrecan and small proteoglycan core proteins, which are turned over by anabolic and catabolic activities in response to external stimuli such as mechanical loading. The ability to perform low turnover repair, however, declines with age.

Chondrocytes are encased in a pericellular matrix (PCM) consisting of collagen VI and other matrix proteins[41]. The PCM helps to maintain the chondrocyte in a differentiated low-turnover state by protecting it from interacting with extracellular matrix components in the inter-territorial cartilage matrix[42,43]. Chondrocytes exist in a low oxygen tension environment and intracellular survival factors such as HIF-1α are required for maintenance of homeostasis and adaptation to the mechanical environment[44]. Primary cilia located on the chondrocyte surface and additional mechanosensitive receptors permit the chondrocytes to sense and adapt their metabolic activity in response to physical forces[42,45].

During the evolution of OA, the cartilage matrix undergoes striking changes in its composition and structure. Initially, surface fibrillations appear and as the pathologic process continues, deep fissures associated with exfoliation of cartilage fragments develop, ultimately leading to delamination and exposure of the underlying calcified cartilage and bone (**Figure 4**). These changes are accompanied by expansion of the zone of calcified cartilage and replacement of the overlying articular cartilage[46-48]. This process is associated with duplication of the tidemark, which is a histologically defined zone that separates the calcified articular cartilage from the underlying calcified cartilage (**Figure 4**). At sites of microcracks and fissures in the osteochondral junction, vascular elements from the marrow space penetrate the subchondral bone and calcified cartilage accompanied by sensory and sympathetic nerves[48]. New bone is formed around these channels recapitulating a program of endochondral bone formation[49,50].

In the early stages of OA, the chondrocytes exhibit increased synthetic activity, reflecting attempts at repair[51]. An early event is the disruption of the chondrocyte PCM exposing the cells to components of the inter-territorial matrix, which, through interaction with cell surface receptors, deregulate chondrocyte function[43]. As the disease progresses, there is depletion of the matrix and the appearance of chondrocytes in clonal clusters consistent with a proliferative response. This is accompanied by the induction of several families of aggrecanases that include members of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family that cleave the aggrecan core protein[52] and several different matrix metalloproteinases (MMPs) (**Table 1**)[53]. Upregulation of genes encoding other proteins associated with inflammatory and catabolic responses also occurs, primarily through signal transduction involving nuclear factor kappa B (NF-κB), mitogen-induced protein kinase (MAPK), and other inflammation- and stress-induced pathways. There is also evidence of increased cell death, which is attributable in part to a decline in autophagy that serves as a protective mechanism used by cells under stress. Many of the chondrocytes also assume a senescence-associated secretory phenotype, characterised by increased production of reactive oxygen species (ROS), cytokines, chemokines and other proinflammatory products.

During the later stages of OA, many of the cells express genes associated with anabolism and chondrocyte hypertrophy[54]. Angiogenic factors, including vascular endothelial growth factor (VEGF), are also present and contribute to the vascular invasion and calcified cartilage expansion occurring at later stages[49,50]. The alterations in the composition of the cartilage extracellular matrix produce marked changes in the material properties of the cartilage and increase its susceptibility to disruption by physical forces. In addition, the matrix degradation products and proinflammatory mediators generated by chondrocyte catabolic activity act in an autocrine or paracrine fashion to further deregulate chondrocyte function but, as discussed below, act on the adjacent synovium to stimulate proliferative and proinflammatory responses.

[H2] Periarticular bone

The bone beneath the articular cartilage is organised into a plate-like layer of cortical bone and a contiguous region of cancellous bone (**Figure 3**)[46,55,56]. They adapt their structure and composition throughout life via cell-mediated processes of remodelling and modelling. Remodelling involves the coordinated activity of osteoclasts that resorb the bone and osteoblasts that mediate bone formation[46]. Modelling involves the addition or removal of bone by osteoclasts or osteoblasts without the coupling of the two processes. Remodelling and modelling provide mechanisms for adapting bone to local biomechanical factors and the influence of systemic hormones and local soluble mediators, and replacing bone that has undergone damage from mechanical injury.

Osteocytes are a third bone cell type. They are distributed throughout cortical and trabecular bone and communicate with osteoclasts and osteoblasts on the bone surface to regulate bone remodelling and modelling[57]. Osteocytes mediate their effects via direct cell-cell signalling and by the release of soluble mediators, including dickkopf-related protein-1 (DKK-1) and sclerostin, which are inhibitors of the Wnt signalling pathway that controls osteoblast differentiation and activity, and receptor activator of NF-κB ligand (RANKL), the principal regulator of osteoclast differentiation and activation, and its inhibitor osteoprotegerin (OPG) (**Figure 5**)[57].

In addition to bone volume and structural organisation, the properties of bone are also affected by its state of mineralization[46,58-60]. Osteoblast-mediated bone formation is initiated by the deposition of unmineralized organic matrix that then undergoes rapid mineralization. This phase is followed by a phase of slow and progressive mineral accretion. In states of high bone turnover, there is an attenuation of the ‘late’ phase of mineral deposition, which leads to a reduction in bone stiffness. In contrast, in low bone turnover states, the continued mineral accretion leads to increased mineralization that is associated with increased bone stiffness. In this way, changes in the rate of bone remodelling and modelling can markedly affect the material properties of bone and its capacity to deform in response to mechanical forces.

OA is accompanied by increases in the volume, thickness and contour of the cortical plate, alterations in the state of bone mineralization and material properties, changes in the subchondral trabecular bone architecture and bone mass, formation of bone cysts, appearance of bone marrow lesions detectible by MRI, and osteophytes (Figures A, B).[55,61-63]. These changes are mediated by alterations in the activity of the bone cells. Bone may also undergo direct physical damage that results in the formation of microcracks or fissures within the cortical or trabecular bone.

Gradual thickening of the subchondral plate is a characteristic feature of advancing OA. These changes reflect the influence of increases in load transfer (**Figure 6**). Importantly, there is a close anatomic association between these bone changes and the development of local OA cartilage pathology[63], indicating that both tissues are responsive to the adverse effects of mechanical loading[64-66]. The changes in cortical plate thickness are accompanied by decreased trabecular bone mass consistent with so called 'stress-shielding' attributable to attenuation of the mechanical forces by the thickened cortical bone plate[61].

Radin and Rose[67] proposed that increased bone stiffness in the subchondral bone adversely affects the overlying cartilage and contributes to the development of OA cartilage pathology. Supporting this concept, Brown *et al.*[65] used a finite element model to analyse the effects of a stiff metal cylinder implanted in the subchondral bone of sheep to predict stress concentrations at the edge of the metal cylinder in the deep cartilage layers. When the cylinder was within the cortical plate, stress concentrations were predicted to increase significantly in the cartilage.

However, studies by Day *et al.*[58,59] challenged the Radin and Rose concept. Using micro-computed tomography (μCT), direct mechanical testing, and finite element analysis of the proximal tibiae from cadaver specimens, they found that although the volume fraction of the subchondral bone was increased, the bone tissue modulus (stiffness) was decreased. They attributed the decreased stiffness to the reduced bone mineral density, related to the increased rate of bone remodelling. They further speculated that the reduction in bone tissue stiffness could lead to increased cartilage deformation during loading, contributing directly to the development of OA cartilage pathology. The study of Brown *et al.*[65] and those of Day *et al.*[58,59] support the concept that alterations in the subchondral bone properties influence the state of the overlying articular cartilage, but indicate the complexity of this relationship, which evolves over the course of OA progression.

[H3] Bone marrow lesions, bone cysts and osteophytes

Bone marrow lesions are regions of increased signal intensity in the subchondral bone detected with fluid sensitive MRI sequences (Figure B)[68]. They were first proposed to represent localised regions of bone marrow edema. However, histologic evaluation reveals the presence of fat necrosis, localised marrow fibrosis, and microfractures of the trabecular bone associated with active bone remodelling and repair[69,70]. The bone marrow lesions tend to associate with regions of OA cartilage pathology and are especially common at sites of denuded cartilage[71].

Subchondral bone cysts are a common feature of advanced OA. The observations that cysts tend to develop at sites of pre-existing bone marrow lesions has led to the concept that they are generated directly within the subchondral bone and that bone damage and necrosis initiates the process of osteoclast-mediated bone resorption that leads to cyst formation[72].

Osteophytes are bony outgrowths that are localised on the joint margins. Studies in animal models suggest they are formed by a process of endochondral ossification[73]. Since the removal of osteophytes increases joint instability in animal models of OA[74], and there is no relationship between structural progression of knee OA and osteophyte size in human subjects with OA, osteophytes may serve to stabilise the joint rather than contributing to the progression of joint pathology[75].

[H2] Synovium

The synovium forms a thin cellular layer lining the joint cavity that acts as a semipermeable membrane to regulate the transfer of molecules in and out of the joint. It is also a major source of the synovial fluid components, which provide nutrients to the chondrocytes and lubricant factors, including lubricin and hyaluronic acid (HA) that contribute to the unique low friction properties of the articular surface. Inflammation, characterised by hyperplasia of the synovial lining and diffuse or perivascular infiltrates of T and B lymphocytes, are common features of OA[76] (**Figure 7**), and imaging studies employing MRI and ultrasound have established a relationship between synovitis and the risk for structural progression of OA and joint symptoms[77-80].

The catabolic processes initiated in the articular cartilage and the deregulated activities of chondrocytes play a key role in the development of the synovial inflammation. Proteinases produced by the chondrocytes lead to the generation of proinflammatory products, which act as damage-associated molecular patterns (DAMPs) that interact with Toll-like receptors (TLRs), integrins and receptor for advanced glycation end-products (RAGEs) expressed on chondrocytes to increase the expression of inflammatory and catabolic products (**Table 1**)[37,76,81,82]. These products are also released into the synovial fluid where they act on the adjacent synovium to induce inflammation that in turn generates additional proinflammatory and catabolic products that feedback on the chondrocytes to further deregulate their function (**Figure 8**). Microarray analysis and Western blotting of OA synovium by Lambert *et al.*[83] identified enhanced expression of key pathways related to angiogenesis, tissue catabolism, inflammation and innate immunity in regions of inflamed versus non-inflamed tissue. The demonstration that cartilage matrix degradation products can activate TLRs provides support for a role of innate immune pathways and mechanisms in OA joint pathology. Ritter *et al.*[84] compared the protein profiles in the synovial fluids from OA and control subjects to the gene expression profiles in OA synovial tissue and cartilage. Three major pathways were identified, including the complement, acute-phase response, and coagulation pathways. Of interest, mice deficient in key complement proteins are partially protected from the development of OA[85].

Multiple proinflammatory cytokines can be detected in OA synovial fluid, cartilage, and synovium[76,86]. Interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF-α) are potent regulators of catabolic processes in chondrocytes and synovial cells, but their roles in OA pathogenesis still need to be established. In our own studies, we detected elevated levels of IL-15, and to a lesser extent IL-6, in synovial fluids and tissues from patients with OA[87]. IL-15 is involved in the recruitment and activation of lymphocytes, and thus could be a contributing factor to the lymphocytic reaction associated with OA synovial inflammation. Many chemokines have been detected in OA synovial fluids and tissues. Their receptors are widely expressed on chondrocytes and synovial cells, implicating a potential role in synovial inflammation in OA[88-90]. Further studies are needed to establish the role of chemokines in OA pathogenesis and to identify them as relevant targets for OA therapy.

[H2] Mechanical factors in the pathogenesis of OA

The preceding sections have highlighted the role of mechanical forces in modulating the activities of the cell types that populate the individual joint tissues. Both physiological and pathological overload forces can affect the biological activity and viability of the resident cell types. At a macroscale level, multiple factors affect the local forces experienced by cells and their extracellular matrices, including joint alignment, kinematics, and aspects of gait that can considerably affect the distribution of load transfer across the joint[91,92]. Joint injuries such as anterior cruciate ligament rupture or loss of integrity of the menisci are examples of conditions that markedly affect the distribution of forces within the joint, but importantly, they result in sustained alterations in joint mechanics that produce long-term effects on cell activity and function. Chondrocytes and osteocytes sense these local biomechanical forces via cellular structures such as primary cilia and a complex system of cell-surface receptors that act as mechanosensors to modulate and adapt the cells to their local biomechanical environment[38,42,45,46]. Compressive forces and tensile strains, as well as osmotic stresses and fluid flow, act on these cell surface sensors to modulate cellular responses via multiple mechanisms including activation of intracellular calcium signalling pathways and modulation of osmolyte channels such as transient receptor potential vanilloid 4 (TRPV4)[91]. These mechanosensors and their downstream signalling pathways represent potential therapeutic targets to modulate the responses of resident cells to mechanical forces to prevent the activation of pathways involved in deregulating remodelling and repair of joint tissues. Many of the mechanotransduction events overlap with those involved in inflammatory stress. Metabolic stress adds another level of complexity, as addressed by Courties et al[93].

[H2] Role of genetic factors in OA pathogenesis

Genetic and epidemiologic studies and Genome Wide Association Studies (GWAS) have helped to establish the important role of genetic factors in the risk for the development of OA and the outcomes and evolution of joint pathology and symptoms[94,95]. Classic twin studies and familial aggregation studies indicate that, after adjustment for known risk factors such as age, sex and BMI, genetic susceptibility for the development of radiographic OA ranges from 40% to 65% depending on the joint site. To date, GWAS have identified multiple common variants associated with knee or hip OA[94], although the individual risk alleles exert only moderate to small effects. Loci associated with OA include genes encoding: components of the transforming growth factor-β (TGF-β) and bone morphogenetic protein (BMP) signalling pathways, including growth/differentiation factor 5 (GDF-5); the type II iodothyronine deiodinase (DIO2) in the thyroid pathway; proteins involved in apoptosis and mitochondrial damage; molecules regulating synthesis and remodelling of extracellular matrix components; WNT signalling pathway components; and proteins associated with inflammation and immune responses. Despite the modest contributions of the individual genetic variants to the increased risk of OA, the identification of these genes has yielded important insight into the molecular mechanisms involved in OA pathogenesis. In addition, this information can be applied to develop biomarkers that can be used to detect individuals at a high risk for the development of OA and to institute preventive or interventional therapies to improve patient outcomes.

[H1] DIAGNOSIS, SCREENING AND PREVENTION

[H2] Diagnosis and screening

Despite the fact that OA is an extremely common illness, it can be difficult to diagnose. Diagnostic criteria were developed for the knee[96,97], hand[98] and hip[99], the primary aim of which was to develop criteria that differentitated OA from other forms of arthritis such as rheumatoid arthritis and ankylosing spondylitis.

[H3] Knee

The clinical criteria include the presence of knee pain in addition to at least three of the following characteristics: i) age greater than 50 years, ii) morning stiffness lasting less than 30 minutes, iii) crepitus on active motion, iv) bony tenderness of the knee, v) bony enlargement, vi) no detectable warmth. Radiographic criteria include knee pain and one of the following: i) age greater than 50 years, ii) morning stiffness lasting less than 30 minutes, iii) crepitus on active motion and osteophytes.

This combination performs with high sensitivity and specificity to differentiate knee OA from other forms of arthritis[96]. It also correlates well with cartilage damage on arthroscopy with radiographic OA showing more damage than clinical[97], presumably reflecting more longstanding disease as radiographic changes can take years to appear. Positioning is crucial to avoid a spurious diagnosis of radiographic OA and there are many ways to achieve this including fluoroscopic and semi flexed radiography.

It is unclear how well these criteria will perform in comparison to healthy elderly subjects, as this was not the aim when they were developed. In clinical practice, patients would often have blood tests to rule out other conditions but these were not necessary in the initial development. Crepitus has recently been shown to be specific to patellofemoral OA with no correlation at all with tibiofemoral disease on MRI scanning[100]. In contrast, an older, smaller, arthroscopy based study reported association with cartilage pathology in both compartments of the knee[101] suggesting it may reflect cartilage pathology which isn’t compartment specific.

There are some limitations to these criteria. Firstly, osteophytes are included in these criteria, which may be a misconception as recent studies suggest the osteophyte is not a key player in the disease process but may be an epiphenomenon[102]. Joint space narrowing and other radiographic features are not part of the criteria despite being considered a key part of the disease in radiographic atlases. Indeed, most OA clinical trials use radiographs for screening purposes, and joint space narrowing is much more common than osteophytes when they are scored separately[103]. Given the lesser degree of cartilage damage with the clinical criteria, it may be that the selection of patients for trials using these criteria may lead to greater potential for response than choosing only patients with radiographic changes. Secondly, many studies have shown a poor correlation between radiographs and symptoms[104], meaning this construct of pain and other features is artificial. This has led to the development of MRI criteria. Recently, Hunter *et al*. conducted a Delphi experiment for defining knee OA on MRI scanning[105]. The diagnostic performance was greatest for osteophytes, cartilage loss, bone marrow lesions and for meniscal tear in any region. This resulted in good specificity for the diagnosis of OA, but less optimal sensitivity, probably owing to detection of disease earlier on MRI. While the individual components of these criteria are relevant for pain and structural change[104], the specific combination in this publication is different for the tibiofemoral and patellofemoral compartments and does not consider pain, Thus, these require validation before widespread acceptance. In addition, pain can come from inside or outside the joint, hence an alternative way of defining this could be: pain and i) any feature within the joint known to lead to cartilage damage (symptomatic OA); ii) any feature outside the joint known to lead to cartilage damage (OA syndrome)[102]. This additional subgrouping may lead to specific therapies based on the source of pain.

[H3] Hand

The criteria for OA of the hand were developed in a similar way to those for the knee in terms of differentiating from other forms of arthritis[98] and have similar issues as the knee. The criteria for hand OA include the presence of hand pain in addition to at least three of the following characteristics: i) bony enlargement of 2 or more of 10 selected joints, ii) bony enlargements of 2 or more DIP joints, iii) fewer than 3 swollen metacarpophalangeal (MCP) joints, iv) deformity of at least 1 of the 10 selected joints.

OA of the hand can often be diagnosed on the basis of these criteria alone, and laboratory tests and X-rays may be unnecessary. Indeed, in the classification of symptomatic OA of the hands[98], radiography was of less value than clinical examination. Data are less well developed for MRI of the hand but it is clear that some of the features commonly seen in the knee are also seen in the hand[106].

[H3] Hip

A patient was classified as having clinical hip OA[99] if pain was present in combination with either: i) hip internal rotation greater than or equal to 15 degrees, pain present on internal rotation of the hip, morning stiffness of the hip for less than or equal to 60 minutes, and age greater than 50 years, or ii) hip internal rotation less than 15 degrees and an erythrocyte sedimentation rate (ESR) less than or equal to 45 mm/hour; if no ESR was obtained, hip flexion less than or equal to 115 degrees was substituted (sensitivity 86%; specificity 75%).

Clinical plus radiographic criteria: The traditional format combined pain with at least 2 of the following 3 criteria: osteophytes (femoral or acetabular), joint space narrowing (superior, axial, and/or medial), and erythrocyte sedimentation rate (ESR) less than 20 mm/hour. In contrast to the hand, the radiographic presence of osteophytes best separated OA patients and controls by the classification tree method.

There are very limited data on hip MRI but preliminary studies suggest bone marrow lesions are much less common than at other sites[107].

[H3] Other sites

No diagnostic criteria for other commonly affected sites such as the spine or big toe have been developed but these are usally diagnosed based on symptoms and/or imaging.

[H3] Diagnosis and screening conclusion

It is easier to diagnose OA clinically when it is well established but difficult in early disease. Imaging can be helpful where there is diagnostic uncertainty. There is increasing data to support the greater sensitivity of MRI over radiographs in early disease. It should be noted that poulation screening programs show that many of the abnormalities seen on imaging are very common in older populations[108], hence these need to be placed in the appropriate clinical context.

[H2] Prevention - What is new?

The most well examined modifiable risk factor for OA is obesity. However, efforts at weight loss have not been effective at a population level, and there has been a steady increase in the prevalence of obesity in most developed and developing countries. In the last decade, significant effort has focused on understanding the mechanisms by which obesity affects the risk of OA. More recent work has also focused on better understanding the effects of physical activity and early life exposures on the risk of OA.

[H3] Obesity – A risk factor for generalised OA that is becoming better understood

As mentioned above, obesity is a well-established risk factor for the development and progression of OA. Nevertheless, while it had been historically considered that the OA-obesity risk may be secondary to excessive joint loading[109], this does not account for the risk of OA in non-weight bearing joints: the risk ratio for being overweight and developing hand OA is 1.9[110]. In weight-bearing joints such as the knee, body fat has been shown to be a better predictor of cartilage loss, independent of fat-free mass.[111] Moreover, the risk of both primary knee and hip joint replacement for OA were three- to four- fold higher in community-based individuals in the highest quartile of fat mass[112] (**Figure 9**).

It is speculated that the effect of adiposity triggers metabolic inflammation, whereby various adipokines induce pro-inflammatory cytokines ultimately leading to cartilage matrix impairment and subchondral bone remodelling[113]. This is supported by in vivo studies, where increased serum adipokines such as leptin and adipsin are associated with greater cartilage loss and higher incidence of knee joint replacement[114,115]. However, while there is a systemic effect of adiposity, local effects have also been observed. Intramuscular quadriceps fat content was found to be a strong predictor of knee cartilage loss[116,117]. In patients with symptomatic knee OA, maintaining muscle size was associated with beneficial structural changes and a reduced risk of knee joint replacement[118].

Weight management therefore remains the most well established primary and secondary preventive strategy for OA. For instance, women who lost an average of 11 pounds decreased their risk for knee OA by 50% in the Framingham Study[119]. In obese adults, as little as 1% change in body weight modified the rate of knee cartilage loss[120], such that avoidance of weight gain could also be an important clinical target in the prevention of knee OA. More specifically, preferential loss of fat, rather than fat-free mass will likely offer the most effective means of preventing OA.

[H3] Physical activity - Implications for primary and secondary prevention of knee OA

There has been a misconception that physical activity may be detrimental to weight-bearing joints. Increasing evidence suggests that physical activity, particularly joint loading, is important for maintaining healthy knee joints. Children who are physically active accrue greater cartilage volume than their more sedentary counterparts[121] while forced immobility (e.g. from spinal cord injury) induces rapid cartilage volume loss in adults[122]. Nevertheless, evidence for whether physical activity is good or bad for joints in community-based adults is conflicting. One reason may be the underlying health of the joint. For example, it has been shown that higher physical activity levels were associated with knee joint replacement secondary to OA[123]. However, vigorous physical activity in pre-clinical populations was associated with increased articular cartilage[124].

It has been hypothesised that joints with structural abnormalities may not be adept at withstanding loads imparted by physical activity. Whereas people with high baseline cartilage volume exposed to occupational and recreational activity reduced their rate of cartilage loss, the same exposure expedited cartilage loss among people with lower baseline cartilage volume[125]. Similarly, greater steps/day were protective against cartilage volume loss in people with more baseline cartilage volume, but increased cartilage loss in those with less baseline cartilage volume[126]. Vigorous physical activity performed on a knee with, but not without, bone marrow lesions was also associated with worsening of medial cartilage defects and a trend toward increased rates of medial tibial cartilage volume loss[127]. While these results were not observed in people with established disease, longitudinal results demonstrating accelerated cartilage loss in pre-clinical populations may inform potential risk factors for incident disease.

Taken together, these data highlight the importance of the underlying health of the knee joint when determining how it may respond to physical activity. While further work is needed to better inform clinical guidelines, advice for physical activity for primary and secondary prevention of knee OA may need to differ. Maintaining physical activity may be important for preventing the development of knee OA, but modification may be required in the presence of joint damage (**Figure 9**).

[H3] Hip OA – Bone shape matters and may be modified in early life

Abnormalities in the shape of the hip bones are central to the pathogenesis of hip OA. Broadly, these can be grouped into hip dysplasia and femoroacetabular impingement (FAI) (**Figure 10**).

Hip dysplasia is defined by insufficient acetabular coverage of the femoral head and results in a concentrated weight-bearing area of the hip joint. Although overt congenital hip dysplasia is a well-recognised risk factor for early hip OA, more subtle degrees of dysplasia have recently been associated with an increased risk of hip OA. For instance, when assessed as a continuous measure, each one degree change toward hip dysplasia increased the 20-year risk of hip joint replacement by 10.5%[128]. Recently, it was speculated that the acetabular underdevelopment that occurs in pre-terms babies[129] may have long-term implications for hip joint health. Indeed, low birth weight and pre-term birth have recently been shown to be associated with an increased risk of hip arthroplasty secondary to OA in later life[130]. Subtle hip dysplasia may be one mechanism mediating this risk. Although requiring further examination, early intervention (e.g. double diapering) may mitigate abnormal hip development in high-risk populations.

FAI occurs when anatomic abnormalities of the femoral head and/or acetabulum result in abnormal contact between the two during hip motion, leading to cartilage damage. The morphometric abnormalities are described by the cam deformity of the femoral head or pincer deformity of the acetabulum. The condition is commonly observed in younger adults and is on the causal pathway to hip OA. For instance, radiographic evidence of FAI in young asymptomatic adults precedes hip OA, with even mild deformity associated with a 3.7 times, and severe deformity a 9.7 times increased risk for end-stage hip OA in later life[131]. Modifiable developmental exposures are also gaining interest. Elite levels of sporting activity during adolescence have been shown to be a risk factor for FAI[132-135], particularly when growth plates are open[134,135]. The mechanism for this has been speculated to be secondary to repetitive joint loading on bones undergoing rapid growth. Similarly, obesity increases hip joint loads and the Nurses' Health Study demonstrated a more than 5-fold increased risk for progressing to hip replacement in later life among 18-year-olds in the highest compared with the lowest body mass index (BMI) categories (≥ 35 kgm-2 and ≤ 22 kgm-2)[136]. Occupations that involve heavy lifting, such as farming, are also a risk factor for hip OA[137]. However, early occupational exposure is important, with a study demonstrating that heavy lifting when aged 18 to 30 was associated with deleterious structural changes of the hip joint in later life[138].

[H2] Prevention of OA – An evolving understanding

Early developmental factors that influence bone shape may be central to the prevention of hip OA, while a tailored approach to physical activity may alter the natural history of knee OA. Weight management remains central to the prevention of OA at various anatomical sites, with a particular focus on maintaining muscle mass while reducing adiposity. Efforts to elucidate preventive strategies in OA continue, with new approaches being identified as we gain a greater understanding of the complexity of the pathogenesis of OA across different joints.

[H1] MANAGEMENT

The management of OA has been described in evidence-based guidelines from important musculoskeletal organisations. These include the UK National Institute for Health and Clinical Excellence (NICE)[139], the American College of Rheumatology (ACR)[140], the European League Against Rheumatism (EULAR)[141-143], the Osteoarthritis Research Society International (OARSI)[144], the European Society for Clinical and Economical Aspects of Osteoporosis and Osteoarthritis and the International Osteoporosis and Other Skeletal Diseases Foundation (ESCEO-IOF)[145] and Cochrane Reviews. There is a general consensus on recommended therapy across these guidelines although discordance exists on particular therapies (**Table 2**). The efficacy of therapies may vary according to the anatomical location and number of joints affected by OA (**Figure 11**); the majority of the evidence base used in writing these guidelines originates from clinical trials of knee OA.

[H2] Initial holistic assessment

Individuals with OA require a comprehensive assessment of the severity and functional impact of

OA along with their health beliefs, to ensure a personalised management strategy is tailored to their needs. This is because better pain and functional outcomes are associated with a patient-centred multidisciplinary approach involving a package of interventions, including self-management strategies. A baseline assessment should include the BMI along with the distribution of joints affected by OA. The involvement of multiple joints and comorbid obesity is prevalent and a poor prognostic phenotype[146,147]. The impact of OA on activities of daily living and employment should also be assessed. The individual's health beliefs, health education needs and motivation for self-management are needed to inform a patient-centred strategy. Assessing these issues may require more than one consultation.

The medical management of OA includes non-pharmacological and pharmacological therapies, and clinicians and people with OA often use multiple therapies.

[H2] Non-pharmacological interventions

Amongst the management guidelines there is a general consensus recommending health education and promotion of self-management. Individuals with OA should understand their individual risk factors (e.g. obesity), their prognosis, and that OA represents failure of joint repair, commonly following one or more joint insults. This insight should be reinforced during serial consultations along with electronic and written information.

Individuals with OA should be encouraged to partake in exercise and be informed of the benefits of this, irrespective of the functional status and structural or pain severity of the OA with which they suffer. Cochrane Reviews report that land-based exercise programs for the hip and knee can improve physical function and pain[148,149] although there is less evidence to indicate hand exercises reduce pain in hand OA. Exercise programs should first aim to improve muscle strength around the affected joints, followed by general aerobic exercise. Indeed, muscle weakness plays a major role in the development of disability, while muscle strengthening is effective at reducing pain and disability[150]. Patient adherence to exercise for OA declines over time, so programs should be tailored to the severity of the OA and involve shared decision making to ensure tolerability and optimise long-term adherence. For example, individuals with significant sarcopenia will benefit from initial low-impact exercises (e.g. walking laps in a swimming pool or cycling on exercise bikes) to strengthen the muscles. This first 'dose' of muscle strengthening exercise should then be titrated up in a patient-centred manner according to the individual's capability.

Individuals who are overweight or obese should be provided with dietary advice or a review by a dietician because weight loss (usually about 10% of body weight) is associated with improved pain and function, though some studies suggest this inhibits the progression of structural changes[119,120,151,152]. Obese individuals attempting weight loss should be encouraged by explaining that improvement in knee OA symptoms follows a dose-response relationship with percentage weight loss[153]. The combination of weight loss and exercise in obese and overweight individuals offers an additive reduction in pain[152].

Aids for OA include adaptation devices, splints and braces. Specific aids are recommended for specific indications by all of the guidelines; this includes splints for base of thumb OA[154,155], devices for opening jars, and walking canes[156]. These can facilitate activities of daily living and reduce OA symptoms. Knee braces can also reduce knee pain and the size of bone marrow lesions in patellofemoral knee OA[157]. Individuals with OA of the lower limbs are recommended to use footwear with thick shock-absorbing soles, no heel elevation, and adequate plantar arch support[141]. Transcutaneous electrical nerve stimulation[158], acupuncture and thermotherapy[159] may be adjuncts for treating OA but are not universally recommended due to the limited evidence supporting their efficacy.

Therefore, a multi-disciplinary, patient-centred combination of education, self-management, exercise, weight loss with realistic goals, encouragement, and regular reassessment is recommended for individuals with OA[141].

[H2] Pharmacological inventions: Topical and oral therapies

Topical, oral and injectable pharmacological treatments are available for individuals with OA. The age, concurrent medications, co-morbid conditions (cardiovascular and gastrointestinal problems in particular) and predicted adherence should be considered for each individual before prescribing a pharmacological intervention. Current therapies are at best moderately effective pain relievers and it is worth noting that studies report that most people with OA have persistent pain despite taking all their prescribed therapies. The effect size of these therapies is summarised in **Table 3**.

First-line therapies include topical non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol[160]. Topical NSAIDs have better safety profiles than oral NSAIDs as systemic drug levels are much lower. They are, however, limited by joint penetration and multiple daily applications. Topical capsaicin is a chilli pepper extract that depletes neurotransmitters in sensory terminals and attenuates the central transmission of peripheral pain impulses from the joint. It is generally recommended as a supplementary analgesic for hand and knee OA and avoids systemic toxicity[160]. Paracetamol is likely a less effective analgesic in OA[161-163].

Oral NSAIDS and selective cyclooxygenase-2 (COX-2) inhibitors are the most common oral pharmacological agents used for treatment of OA. They are associated with significant toxicities (gastrointestinal and cardiovascular in particular) especially with increasing age and co-morbidities. Opioids are variably used across countries, though often remain the only option for people who cannot tolerate or should not be exposed to NSAIDs. However, they bring their own considerable toxicity profile (including dizziness, nausea, constipation and falls). There is limited evidence for the use of duloxetine, a serotonin-norepinephrine reuptake inhibitor, in knee OA; the OARSI and ACR guidelines recommend its use in multi-joint OA and knee OA, respectively. In the US (but not Europe) duloxetine is licensed for musculoskeletal pain.

Nutraceuticals, including glucosamine and chondroitin sulfate products, are natural compounds consisting of GAG unit components and GAGs, respectively. These are not recommended by some existing guidelines[139,140,144] due to the lack of certainty of clinically important analgesic benefit, whereas Cochrane Reviews and ESCEO guidelines conclude these therapies may have analgesic effects beyond the placebo effect[145,164,165]. However, more recent observational and trial evidence indicates their potential as both an effective analgesic[166] and for attenuation of structural progression[167,168]. There remains controversy regarding the efficacy of nutraceuticals in OA.

[H2] Intra-articular therapies

Individuals with moderate to severe OA pain may derive short-term analgesic benefits with intra-articular corticosteroids, presumably due to their anti-inflammatory actions. They may be used in patients in whom pain is preventing appropriate muscle strengthening exercise, or more uncommonly where large effusions are painful or limit joint movement. HA or hyaluronan is a high molecular-weight GAG, a naturally occurring component of synovial fluid and cartilage. It provides the viscoelastic properties of synovial fluid that may provide lubricating and shock absorbing properties. HA use in knee OA is conditionally recommended by the ACR (2012) guidelines[140] in individuals with knee OA over the age of 74, with symptoms refractory to standard pharmacological treatments. The NICE and OARSI guidelines (2014) do not recommend HA and were informed by a larger literature review and health economic evaluation. This conclusion is supported by a meta-analysis (2012) of the therapeutic benefit of HA in knee OA, which states the benefit is small and clinically irrelevant[169].

[H2] Follow up and review

The guidelines do not generally comment on follow up. However, the NICE guidance recommended regular reviews especially where refractory and disturbing joint pain exists, where there is greater than one symptomatic joint or co-morbidity, and where regular oral medications require monitoring (full blood count, renal function). The frequency of follow up should be agreed upon between the patient and the practitioner in conjunction with sensible goal-setting. Follow up should also present an opportunity to reassess and reinforce important education and self-management messages and titrate therapies, and monitor for efficacy and toxicity.

[H2] Referral for consideration of joint surgery

Arthroscopic lavage and debridement are not recommended for knee OA treatment, without a clear history of true mechanical locking, because the clinical outcomes are not improved[146]. However, if the medical interventions described above fail to sufficiently improve persistent debilitating symptoms of OA, joint replacement surgery should be considered. Joint replacement surgery has been very highly effective for the hip and increasingly so for knee joint; the evidence for other joint replacements lags behind. The individual with OA should be adequately informed regarding the relative benefits and risks of further medical versus prospective surgical options along with a realistic understanding of the postsurgical rehabilitation. Individuals considering knee replacement should be reviewed for independent risk factors for persistent pain occurring after total knee replacement. The strongest preoperative predictors of this complication include mental health disorders, catastrophising, pain at multiple sites and preoperative knee pain[170]. The optimal time for a surgical referral should be before an established functional limitation or severe pain occurs**.** In younger patients, surgery may be delayed because joint prostheses have a finite life expectancy and revision surgery offers less favourable outcomes.

[H2] Structure modification

Therapies that confer a cessation or inhibition of structural deterioration of knee cartilage are highly desirable. However, conclusive evidence of a structure-modifying therapy is lacking despite a number of randomised placebo controlled trials that report having achieved this. These included chondroitin sulfate, glucosamine sulfate[167,168,171-173], and strontium ranelate[174]. There are currently no licensed structure-modifying therapies.

[H1] QUALITY OF LIFE

[H2] Morbidity

The lifetime risk of OA-specific morbidity is about 25% for the hip and 45% for the knee; the disorder is a major contributor to the 57,000 knee and 55,000 hip arthroplasties undertaken each year in the United Kingdom[175-177]. In the 2010 World Health Organisation (WHO) Global Burden of Disease Study, OA was the 11th highest cause of years lived with disability worldwide; this represented a rise from 15th position in the 1990 study[178,179]. The disorder is associated with a major impact on activity limitation[180], especially walking (22%), but also affects daily living activities such as dressing (12.8%) and carrying heavy objects (18.6%). In European studies[181], around 11.8% of affected individuals require assistance in care from health professionals, 9.2% require assistance from immediate family; and 8.9% of health service delivery is directly attributable to the disorder. The pain and loss of function account for a substantial economic burden, with estimates typically ranging from around 1.0 to 2.5% of gross domestic product in Western nations[176].

[H2] Mortality

Patients with OA are at greater risk of premature death than comparable controls from the general population[182]. In a large population-based sample of British men and women[183] with symptomatic, radiographically evident OA of the knee and hip, all-cause mortality was significantly elevated (standard mortality ratio (SMR) 1.55, 95%CI 1.41-1.70). Cause-specific mortality was particularly high for cardiovascular disease and dementia, possibly through low grade systemic inflammation, long term use of NSAIDs, or physical inactivity. These findings were replicated in a Canadian cohort study, where elevated all-cause mortality was associated with baseline functional limitation[184], as well as in the US Study of Osteoporotic Fractures[185], which detected an excess risk of all-cause (hazard ratio (HR) 1.14; 1.05-1.24) and cardiovascular (HR 1.24; 1.09-1.41) mortality. While associations with cardiovascular risk factors, most notably obesity, insulin resistance, and hypertension might explain part of the effect of OA on premature death, novel pathways that lead to accelerated biological senescence present an intriguing additional possibility. However, those with function loss in some of these studies appear to have a selective increase in mortality, and it remains possible that the finding may not be disease-specific.

[H1] OUTLOOK (Box 1)

OA is among the diseases with the fastest growing incidence, which is mainly due to the aging of the world population[186]. The burden of this very chronic, crippling and debilitating disease is an enormous challenge for the healthcare system and society in general, related to the direct cost of the disease and all the indirect costs generated by it, not to mention that OA is now recognised as an independent risk factor for increased mortality[182,187]. These findings clearly demonstrate the importance of developing effective treatments that can not only reduce symptoms but also slow or stop the disease progression[188]. Significant investment in basic and clinical research over the last few decades has provided important clues about the risk factors associated with the disease development and progression. New findings with regard to the disease pathophysiology have enabled a better understanding of the disease process and identified potential therapeutic targets[189]. Much work, however, remains to be done to understand how we can integrate these findings into a final and comprehensive concept that can explain the chronological steps of the development of OA. The basic research findings need to be comprehensively integrated with those from clinical research in order to provide a global, and clearer, picture of the disease process. Hence, significant new findings from epidemiological, observational, genetic, epigenetic and clinical studies, including those that have explored structural changes using imaging technologies such as MRI, have provided a large body of new information about risk factors associated with OA progression, which complement those generated from basic science research[19,188] integrating a translational approach to OA research. This makes it possible to move the research focus from observational to interventional, which is the main challenge of the next decade in this field of research, with emphasis on the development of disease-modifying OA drug

(DMOAD) treatments. Prevention should remain an important dimension of the management of OA. Observational studies such as the Osteoarthritis Initiative (OAI)[190], the Tasmanian older adult cohort (TASOAC)[191] and others have helped provide valuable information in that respect and hopefully more will come from ongoing and future observational studies.

The therapeutic options for OA treatment as mentioned are still for the most part symptomatic and no DMOAD treatment has yet received regulatory approval. The development of safe and effective new treatments for OA is the main challenge of the future. The recent safety issues surrounding NSAIDs and acetaminophen have unfortunately left clinicians with even fewer options for the treatment of OA patients[163,192]. Symptomatic slow-acting drugs for OA (SYSADOAs), local and topical, could be helpful but more new drugs/agents are desperately needed[145]. The recent advances in understanding the pain mechanisms in OA should be of help in the development of more targeted therapy with improved benefit-to-risk balance that can also improve the quality of life of patients. There is also a need for developing new tools that can help predict which patients should present a better response to a specific treatment[193]. Personalised medicine is becoming a priority and should include OA treatment[194-197]. The strategy regarding treatment of OA symptoms should focus on, in addition to the pain itself, factors that may be responsible for its modulation, particularly in older patients.

The ultimate goal of future therapeutic development in OA is to target treatments that will not only improve symptoms but at the same time reduce or stop disease progression (DMOADs)[19,188]. However, OA is a more complex disease than previously assumed and it is believed to involve multiple phenotypes/subgroups. Identifying phenotypes will also likely help the development of approaches to non-pharmacological management of OA as well as other treatment modalities as, for example, a depressive OA phenotype has recently been identified, which may need targeted treatment[198]. It is now of the utmost importance to move this therapeutic field forward; selectively targeting some phenotypes of OA patients may allow the development of DMOADs based on personalised medicine. We need to look closely at past experience and take steps to improve upon what we have learned. This topic, which is the subject of recent review articles[19,188], remains the same today. There are several important issues that need to be addressed, including the heterogeneity between studies and regulatory guidelines. Clinical trial protocols should be better standardised and more uniform[188].

Much emphasis has been placed on studying the weight-bearing joints. Since OA is very often a generalised disease, the question as to what should be the primary outcome of DMOAD studies, as well as which OA patient subgroups to include, should be revisited. Moreover, the issue of DMOADs being required to have the dual action of symptomatic efficacy should be comprehensive of an improvement in quality of life and well-being of patients, rather than focusing primarily on pain. Study outcome measures as defined today by regulatory bodies are not optimal in view of the recent advances in OA research[199]. These should be updated, taking into account recommendations from different groups of experts looking at defining “responder criteria.”

Reducing DMOAD study duration and the number of patients needed in DMOAD trials can likely be achieved with the use of advanced imaging technologies such as MRI rather than X-rays[19]. As in many other fields of medical research, this should allow for significant saving, making DMOAD development programs more accessible[19].

In summary, OA remains one of the most challenging chronic diseases. Its steadily increasing prevalence, impact on the quality of life of an aging population, and economic burden provide a strong rationale for the urgent need for increasing the investment made to better understanding and dealing with disease symptoms and joint structure damage. Much has been accomplished but much remains to be done. This is particularly true with regard to developing new drugs and agents that can improve disease symptoms at the same time as reduce joint destruction.

Box 1.

SIGNIFICANT PROGRESS MADE IN:

- Pathophysiology
- Identifying impact of disease on quality of life
- Risk factors associated with disease development/progression
- Imaging technology to assess structural changes and progression
- Treatment of disease symptoms

MAJOR CHALLENGES REMAINING:

- Targeted development of new, effective and safe symptomatic and disease-modifying treatment (DMOAD)
- Identification of biomarkers to predict disease development/progression
- Optimisation and uniformity of clinical trial protocol design
- Updating by the regulatory bodies of clinical trial guidelines for the conduct of DMOAD trials including defining study outcomes

AUTHOR CONTRIBUTIONS

Introduction (JM-P, J-PP); Epidemiology (CC); Mechanisms/pathophysiology (MBG, SRG); Diagnosis, screening and prevention (FMC, GJ, AJT); Management (AJB, PGC); Quality of life (CC); Outlook (JM-P, J-PP); overview of Primer (JM-P, J-PP).

COMPETING INTERESTS

JM-P – Shareholder: ArthroLab Inc. Consultant: AbbVie, Bioibérica, Ferring, Medapharma, Pierre-Fabre, TRB Chemedica.

PGC – Speakers Bureau or consultant for AbbVie, Flexion, Janssen, Lilly, Novartis, Pfizer, Regeneron, Roche.

CC has received consultancy fees and honoraria from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB.

J-PP – Shareholder: ArthroLab Inc. Consultant: AbbVie, Bioibérica, Centrexion, Ferring, Medapharma, Pfizer, Pierre-Fabre, Teva Pharmaceuticals, TRB Chemedica.

AJB, FMC, MBG, SRG, GJ, AJT declare no competing interests.

REFERENCES

1. Wells, C. The palaeopathology of bone disease. *Practitioner* **210**, 384-91 (1973).
2. Majno, G. Man and Wound in the Ancient World (Harvard University Press, Cambridge, MA, 1975).
3. Straus, W.L., Jr. & Cave, J.E. Pathology and the posture of Neanderthal man. *Q Rev Biol* **32**, 348-63 (1957).
4. Ackerknecht, E.H. in Anthropology Today: An Encyclopedic Inventory (ed. Kroeber, A.L.) 120-126 (University of Chicago Press, Chicago, IL, 1953).
5. Braunstein, E.M., White, S.J., Russell, W. & Harris, J.E. Paleoradiologic evaluation of the Egyptian royal mummies. *Skeletal Radiol* **17**, 348-52 (1988).
6. Rogers, J., Watt, I. & Dieppe, P. Arthritis in Saxon and mediaeval skeletons. *Br Med J (Clin Res Ed)* **283**, 1668-70 (1981).
7. Karsh, R.S. & McCarthy, J.D. Archeology and Arthritis. *AMA Arch Intern Med* **105**, 640-644 (1960).
8. Heberden, W. Commentaries on the History and Cure of Diseases (ed. Payne, T.) (London, 1802).
9. Garrod, A.B. The Nature and Treatment of Gout and Rheumatic Gout (Walton and Maberly, London, 1859).
10. Arden, N. & Cooper, C. in Osteoarthritis Handbook (eds. Arden, N. & Cooper, C.) 1-22 (Taylor and Francis, Abingdon, U.K., 2006).
11. Sellam, J. & Berenbaum, F. Is osteoarthritis a metabolic disease? *Joint Bone Spine* **80**, 568-73 (2013).
12. Spector, T.D., Cicuttini, F., Baker, J., Loughlin, J. & Hart, D. Genetic influences on osteoarthritis in women: a twin study. *BMJ* **312**, 940-3 (1996).
13. Bijkerk, C. *et al.* Heritabilities of radiologic osteoarthritis in peripheral joints and of disc degeneration of the spine. *Arthritis Rheum* **42**, 1729-35 (1999).
14. Zhai, G. *et al.* The genetic contribution to muscle strength, knee pain, cartilage volume, bone size, and radiographic osteoarthritis: a sibpair study. *Arthritis Rheum* **50**, 805-10 (2004).
15. Rodriguez-Fontenla, C. *et al.* Assessment of osteoarthritis candidate genes in a meta-analysis of nine genome-wide association studies. *Arthritis Rheumatol* **66**, 940-9 (2014).
16. Valdes, A.M. *et al.* The GDF5 rs143383 polymorphism is associated with osteoarthritis of the knee with genome-wide statistical significance. *Ann Rheum Dis* **70**, 873-5 (2011).
17. Flores, R.H. & Hochberg, M.C. in Osteoarthritis (eds. Brandt, K.D., Doherty, M. & Lohmander, L.S.) 1-8 (Oxford University Press, Oxford, U.K., 2003).
18. Spector, T.D. & Cooper, C. Radiographic assessment of osteoarthritis in population studies: whither Kellgren and Lawrence? *Osteoarthritis Cartilage* **1**, 203-6 (1993).
19. Pelletier, J.P. *et al.* What is the predictive value of MRI for the occurrence of knee replacement surgery in knee osteoarthritis? *Ann Rheum Dis* **72**, 1594-604 (2013).
20. Dennison, E. & Cooper, C. in Textbook of Osteoarthritis (eds. Brandt, K.D., Doherty, M. & Lohmander, L.S.) 227-223 (Oxford University Press, Oxford, U.K., 2003).
21. Roos, E.M. Hip dysfunction and osteoarthritis outcome score (HOOS). Available at http://www.koos.nu (Accessed 2016-06-21).
22. Roos, E.M. & Lohmander, L.S. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes* **1**, 64 (2003).
23. Felson, D.T. in Osteoarthritis (eds. Brandt, K.D., Doherty, M. & Lohmander, L.S.) 9-16 (Oxford University Press, Oxford, U.K., 2003).
24. Kellgren, J.H. & Lawrence, J.S. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* **16**, 494-502 (1957).

25. Felson, D.T. *et al.* The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* **30**, 914-8 (1987).
26. van Saase, J.L., van Romunde, L.K., Cats, A., Vandenbroucke, J.P. & Valkenburg, H.A. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis* **48**, 271-80 (1989).
27. Cooper, C. *et al.* Generalized osteoarthritis in women: pattern of joint involvement and approaches to definition for epidemiological studies. *J Rheumatol* **23**, 1938-42 (1996).
28. Johnson, V.L. & Hunter, D.J. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol* **28**, 5-15 (2014).
29. Oliveria, S.A., Felson, D.T., Reed, J.I., Cirillo, P.A. & Walker, A.M. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis Rheum* **38**, 1134-41 (1995).
30. Prieto-Alhambra, D. *et al.* Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. *Ann Rheum Dis* **73**, 1659-64 (2014).
31. Cooper, C. *et al.* Risk factors for the incidence and progression of radiographic knee osteoarthritis. *Arthritis Rheum* **43**, 995-1000 (2000).
32. Palazzo, C., Nguyen, C., Lefevre-Colau, M.M., Rannou, F. & Poiraudeau, S. Risk factors and burden of osteoarthritis. *Ann Phys Rehabil Med*, http://dx.doi.org/10.1016/jrehab.2016.01.006 (2016).
33. Zhang, Y. *et al.* Methodologic challenges in studying risk factors for progression of knee osteoarthritis. *Arthritis Care Res (Hoboken)* **62**, 1527-32 (2010).
34. Veronese, N. *et al.* Osteoarthritis and mortality: A prospective cohort study and systematic review with meta-analysis. *Semin Arthritis Rheum* (2016).
35. Goldring, S.R. & Goldring, M.B. in Kelly's Textbook of Rheumatology (eds. Firestein, G.S., Budd, R.C., Gabriel, S.E., McInnes, I.B. & O'Dell, J.R.) Chapter 1: 1-19 (Saunders, an imprint of Elsevier, Inc., Philadelphia, PA., 2013).
36. Heinegard, D. & Saxne, T. The role of the cartilage matrix in osteoarthritis. *Nat Rev Rheumatol* **7**, 50-6 (2011).
37. Houard, X., Goldring, M.B. & Berenbaum, F. Homeostatic mechanisms in articular cartilage and role of inflammation in osteoarthritis. *Curr Rheumatol Rep* **15**, 375 (2013).
38. Quinn, T.M., Hauselmann, H.J., Shintani, N. & Hunziker, E.B. Cell and matrix morphology in articular cartilage from adult human knee and ankle joints suggests depth-associated adaptations to biomechanical and anatomical roles. *Osteoarthritis Cartilage* **21**, 1904-12 (2013).
39. Andriacchi, T.P. & Favre, J. The nature of in vivo mechanical signals that influence cartilage health and progression to knee osteoarthritis. *Curr Rheumatol Rep* **16**, 463 (2014).
40. Guo, H., Maher, S.A. & Torzilli, P.A. A biphasic finite element study on the role of the articular cartilage superficial zone in confined compression. *J Biomech* **48**, 166-70 (2015).
41. Wilusz, R.E., Sanchez-Adams, J. & Guilak, F. The structure and function of the pericellular matrix of articular cartilage. *Matrix Biol* **39**, 25-32 (2014).
42. Loeser, R.F. Integrins and chondrocyte-matrix interactions in articular cartilage. *Matrix Biol* **39**, 11-6 (2014).
43. Xu, L., Golshirazian, I., Asbury, B.J. & Li, Y. Induction of high temperature requirement A1, a serine protease, by TGF-beta1 in articular chondrocytes of mouse models of OA. *Histol Histopathol* **29**, 609-18 (2014).
44. Maes, C. *et al.* VEGF-independent cell-autonomous functions of HIF-1alpha regulating oxygen consumption in fetal cartilage are critical for chondrocyte survival. *J Bone Miner Res* **27**, 596-609 (2012).

45. Ruhlen, R. & Marberry, K. The chondrocyte primary cilium. *Osteoarthritis Cartilage* **22**, 1071-6 (2014).
46. Burr, D.B. Anatomy and physiology of the mineralized tissues: role in the pathogenesis of osteoarthrosis. *Osteoarthritis Cartilage* **12 Suppl A**, S20-30 (2004).
47. Burr, D.B. & Schaffler, M.B. The involvement of subchondral mineralized tissues in osteoarthrosis: quantitative microscopic evidence. *Microsc Res Tech* **37**, 343-57 (1997).
48. Imhof, H. *et al.* Subchondral bone and cartilage disease: a rediscovered functional unit. *Invest Radiol* **35**, 581-8 (2000).
49. Walsh, D.A. *et al.* Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. *Rheumatology (Oxford)* **49**, 1852-61 (2010).
50. Suri, S. & Walsh, D.A. Osteochondral alterations in osteoarthritis. *Bone* **51**, 204-11 (2012).
51. Lohmander, L.S., Saxne, T. & Heinegard, D.K. Release of cartilage oligomeric matrix protein (COMP) into joint fluid after knee injury and in osteoarthritis. *Ann Rheum Dis* **53**, 8-13 (1994).
52. Fosang, A.J. & Beier, F. Emerging Frontiers in cartilage and chondrocyte biology. *Best Pract Res Clin Rheumatol* **25**, 751-66 (2011).
53. Wang, M. *et al.* MMP13 is a critical target gene during the progression of osteoarthritis. *Arthritis Res Ther* **15**, R5 (2013).
54. Sandell, L.J. Etiology of osteoarthritis: genetics and synovial joint development. *Nat Rev Rheumatol* **8**, 77-89 (2012).
55. Goldring, S.R. Role of bone in osteoarthritis pathogenesis. *Med Clin North Am* **93**, 25-35, xv (2009).
56. Goldring, M.B. & Goldring, S.R. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. *Ann N Y Acad Sci* **1192**, 230-7 (2010).
57. Dallas, S.L., Prideaux, M. & Bonewald, L.F. The osteocyte: an endocrine cell ... and more. *Endocr Rev* **34**, 658-90 (2013).
58. Day, J.S. *et al.* Adaptation of subchondral bone in osteoarthritis. *Biorheology* **41**, 359-68 (2004).
59. Day, J.S. *et al.* A decreased subchondral trabecular bone tissue elastic modulus is associated with pre-arthritic cartilage damage. *J Orthop Res* **19**, 914-8 (2001).
60. Couchourel, D. *et al.* Altered mineralization of human osteoarthritic osteoblasts is attributable to abnormal type I collagen production. *Arthritis Rheum* **60**, 1438-50 (2009).
61. Burr, D.B. & Gallant, M.A. Bone remodelling in osteoarthritis. *Nat Rev Rheumatol* **8**, 665-73 (2012).
62. Goldring, S.R. The role of bone in osteoarthritis pathogenesis. *Rheum Dis Clin North Am* **34**, 561-71 (2008).
63. Raynauld, J.P. *et al.* Correlation between bone lesion changes and cartilage volume loss in patients with osteoarthritis of the knee as assessed by quantitative magnetic resonance imaging over a 24-month period. *Ann Rheum Dis* **67**, 683-8 (2008).
64. Ko, F.C. *et al.* In vivo cyclic compression causes cartilage degeneration and subchondral bone changes in mouse tibiae. *Arthritis Rheum* **65**, 1569-78 (2013).
65. Brown, T.D., Radin, E.L., Martin, R.B. & Burr, D.B. Finite element studies of some juxtarticular stress changes due to localized subchondral stiffening. *J Biomech* **17**, 11-24 (1984).
66. Poulet, B., Hamilton, R.W., Shefelbine, S. & Pitsillides, A.A. Characterizing a novel and adjustable noninvasive murine joint loading model. *Arthritis Rheum* **63**, 137-47 (2011).
67. Radin, E.L. & Rose, R.M. Role of subchondral bone in the initiation and progression of cartilage damage. *Clin Orthop Relat Res*, 34-40 (1986).
68. Wilson, A.J., Murphy, W.A., Hardy, D.C. & Totty, W.G. Transient osteoporosis: transient bone marrow edema? *Radiology* **167**, 757-60 (1988).

69. Taljanovic, M.S. *et al.* Bone marrow edema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination, radiographic findings, and histopathology. *Skeletal Radiol* **37**, 423-31 (2008).
70. Leydet-Quilici, H. *et al.* Advanced hip osteoarthritis: magnetic resonance imaging aspects and histopathology correlations. *Osteoarthritis Cartilage* **18**, 1429-35 (2010).
71. Bowes, M.A. *et al.* Osteoarthritic bone marrow lesions almost exclusively colocate with denuded cartilage: a 3D study using data from the Osteoarthritis Initiative. *Ann Rheum Dis*, DOI: 10.1136/annrheumdis-2015-208407 [Epub ahead of print] (2015).
72. Crema, M.D. *et al.* Subchondral cystlike lesions develop longitudinally in areas of bone marrow edema-like lesions in patients with or at risk for knee osteoarthritis: detection with MR imaging--the MOST study. *Radiology* **256**, 855-62 (2010).
73. van der Kraan, P.M. & van den Berg, W.B. Osteophytes: relevance and biology. *Osteoarthritis Cartilage* **15**, 237-44 (2007).
74. Pottenger, L.A., Phillips, F.M. & Draganich, L.F. The effect of marginal osteophytes on reduction of varus-valgus instability in osteoarthritic knees. *Arthritis Rheum* **33**, 853-8 (1990).
75. Felson, D.T. *et al.* Osteophytes and progression of knee osteoarthritis. *Rheumatology (Oxford)* **44**, 100-4 (2005).
76. Scanzello, C.R. & Goldring, S.R. The role of synovitis in osteoarthritis pathogenesis. *Bone* **51**, 249-257 (2012).
77. Baker, K. *et al.* Relation of synovitis to knee pain using contrast-enhanced MRIs. *Ann Rheum Dis* **69**, 1779-83 (2010).
78. Felson, D.T. *et al.* Synovitis and the risk of knee osteoarthritis: the MOST Study. *Osteoarthritis Cartilage* **24**, 458-64 (2016).
79. Roemer, F.W. *et al.* Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. *Ann Rheum Dis* **70**, 1804-9 (2011).
80. Pelletier, J.P. *et al.* A new non-invasive method to assess synovitis severity in relation to symptoms and cartilage volume loss in knee osteoarthritis patients using MRI. *Osteoarthritis Cartilage* **16 Suppl 3**, S8-13 (2008).
81. Loeser, R.F., Goldring, S.R., Scanzello, C.R. & Goldring, M.B. Osteoarthritis: A disease of the joint as an organ. *Arthritis Rheum* **64**, 1697-707 (2012).
82. Liu-Bryan, R. & Terkeltaub, R. Emerging regulators of the inflammatory process in osteoarthritis. *Nat Rev Rheumatol* **11**, 35-44 (2015).
83. Lambert, C. *et al.* Gene expression pattern of cells from inflamed and normal areas of osteoarthritis synovial membrane. *Arthritis Rheumatol* **66**, 960-8 (2014).
84. Ritter, S.Y. *et al.* Proteomic analysis of synovial fluid from the osteoarthritic knee: comparison with transcriptome analyses of joint tissues. *Arthritis Rheum* **65**, 981-92 (2013).
85. Wang, Q. *et al.* Identification of a central role for complement in osteoarthritis. *Nat Med* **17**, 1674-9 (2011).
86. Kapoor, M., Martel-Pelletier, J., Lajeunesse, D., Pelletier, J.P. & Fahmi, H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* **7**, 33-42 (2011).
87. Scanzello, C.R. *et al.* Local cytokine profiles in knee osteoarthritis: elevated synovial fluid interleukin-15 differentiates early from end-stage disease. *Osteoarthritis Cartilage* **17**, 1040-8 (2009).
88. Cuellar, J.M., Scuderi, G.J., Cuellar, V.G., Golish, S.R. & Yeomans, D.C. Diagnostic utility of cytokine biomarkers in the evaluation of acute knee pain. *J Bone Joint Surg Am* **91**, 2313-20 (2009).

89. Scanzello, C.R. *et al.* Synovial inflammation in patients undergoing arthroscopic meniscectomy: molecular characterization and relationship to symptoms. *Arthritis Rheum* **63**, 391-400 (2011).
90. Takebe, K., Rai, M.F., Schmidt, E.J. & Sandell, L.J. The chemokine receptor CCR5 plays a role in post-traumatic cartilage loss in mice, but does not affect synovium and bone. *Osteoarthritis Cartilage* **23**, 454-61 (2015).
91. Varady, N.H. & Grodzinsky, A.J. Osteoarthritis year in review 2015: mechanics. *Osteoarthritis Cartilage* **24**, 27-35 (2016).
92. Bennell, K.L. *et al.* Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. *Ann Rheum Dis* **70**, 1770-4 (2011).
93. Courties, A., Gualillo, O., Berenbaum, F. & Sellam, J. Metabolic stress-induced joint inflammation and osteoarthritis. *Osteoarthritis Cartilage* **23**, 1955-65 (2015).
94. Valdes, A.M. & Spector, T.D. Genetic epidemiology of hip and knee osteoarthritis. *Nat Rev Rheumatol* **7**, 23-32 (2011).
95. Tsezou, A. Osteoarthritis year in review 2014: genetics and genomics. *Osteoarthritis Cartilage* **22**, 2017-24 (2014).
96. Altman, R. *et al.* Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* **29**, 1039-49 (1986).
97. Wu, C.W. *et al.* Validation of American College of Rheumatology classification criteria for knee osteoarthritis using arthroscopically defined cartilage damage scores. *Semin Arthritis Rheum* **35**, 197-201 (2005).
98. Altman, R. *et al.* The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* **33**, 1601-10 (1990).
99. Altman, R. *et al.* The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum* **34**, 505-14 (1991).
100. Schiphof, D. *et al.* Crepitus is a first indication of patellofemoral osteoarthritis (and not of tibiofemoral osteoarthritis). *Osteoarthritis Cartilage* **22**, 631-8 (2014).
101. Ike, R. & O'Rourke, K.S. Compartment-directed physical examination of the knee can predict articular cartilage abnormalities disclosed by needle arthroscopy. *Arthritis Rheum* **38**, 917-25 (1995).
102. Jones, G. What's new in osteoarthritis pathogenesis? *Intern Med J* **46**, 229-36 (2016).
103. Zhai, G. *et al.* Correlates of knee pain in older adults: Tasmanian Older Adult Cohort Study. *Arthritis Rheum* **55**, 264-71 (2006).
104. Bedson, J. & Croft, P.R. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord* **9**, 116 (2008).
105. Hunter, D.J. *et al.* Definition of osteoarthritis on MRI: results of a Delphi exercise. *Osteoarthritis Cartilage* **19**, 963-9 (2011).
106. Haugen, I.K. *et al.* Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann Rheum Dis* **71**, 899-904 (2012).
107. Ahedi, H., Aitken, D., Blizzard, L., Cicuttini, F. & Jones, G. A population-based study of the association between hip bone marrow lesions, high cartilage signal, and hip and knee pain. *Clin Rheumatol* **33**, 369-76 (2014).
108. Guermazi, A. *et al.* Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). *BMJ* **345**, e5339 (2012).
109. Felson, D.T., Goggins, J., Niu, J., Zhang, Y. & Hunter, D.J. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. *Arthritis Rheum* **50**, 3904-9 (2004).

110. Yusuf, E. *et al.* Association between weight or body mass index and hand osteoarthritis: a systematic review. *Ann Rheum Dis* **69**, 761-5 (2010).
111. Ding, C., Stannus, O., Cicuttini, F., Antony, B. & Jones, G. Body fat is associated with increased and lean mass with decreased knee cartilage loss in older adults: a prospective cohort study. *Int J Obes (Lond).* **37**, 822-7 (2013).
112. Wang, Y. *et al.* Relationship between body adiposity measures and risk of primary knee and hip replacement for osteoarthritis: a prospective cohort study. *Arthritis Res Ther* **11**, R31 (2009).
113. Wang, X., Hunter, D., Xu, J. & Ding, C. Metabolic triggered inflammation in osteoarthritis. *Osteoarthritis Cartilage* **23**, 22-30 (2015).
114. Stannus, O.P. *et al.* Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults. *Ann Rheum Dis* **74**, 82-8 (2015).
115. Martel-Pelletier, J., Raynauld, J.P., Dorais, M., Abram, F. & Pelletier, J.P. The levels of the adipokines adipsin and leptin are associated with knee osteoarthritis progression as assessed by MRI and incidence of total knee replacement in symptomatic osteoarthritis patients: a post hoc analysis. *Rheumatology (Oxford)* **55**, 680-8 (2016).
116. Teichtahl, A.J. *et al.* Vastus medialis fat infiltration - a modifiable determinant of knee cartilage loss. *Osteoarthritis Cartilage* **23**, 2150-7 (2015).
117. Raynauld, J.P. *et al.* Magnetic Resonance Imaging-Assessed Vastus Medialis Muscle Fat Content and Risk for Knee Osteoarthritis Progression: Relevance From a Clinical Trial. *Arthritis Care Res (Hoboken)* **67**, 1406-15 (2015).
118. Wang, Y. *et al.* Increase in vastus medialis cross-sectional area is associated with reduced pain, cartilage loss, and joint replacement risk in knee osteoarthritis. *Arthritis Rheum* **64**, 3917-25 (2012).
119. Felson, D.T., Zhang, Y., Anthony, J.M., Naimark, A. & Anderson, J.J. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study [see comments]. *Ann Intern Med* **116**, 535-9 (1992).
120. Teichtahl, A.J. *et al.* Weight change and change in tibial cartilage volume and symptoms in obese adults. *Ann Rheum Dis* **74**, 1024-9 (2015).
121. Jones, G., Ding, C., Glisson, M., Hynes, K. & Ma, D. Cartilage development in children: a longitudinal study of the effect of sex, growth, body composition and physical activity. *Pediatr Res* **54**, 230-6 (2003).
122. Vanwanseele, B., Eckstein, F., Knecht, H., Spaepen, A. & Stussi, E. Longitudinal analysis of cartilage atrophy in the knees of patients with spinal cord injury. *Arthritis Rheum* **48**, 3377-81 (2003).
123. Wang, Y. *et al.* Is physical activity a risk factor for primary knee or hip replacement due to osteoarthritis? A prospective cohort study. *J Rheumatol* **38**, 350-7 (2011).
124. Racunica, T. *et al.* Effect of physical activity on articular knee joint structures in community-based adults. *Arthritis Rheum* **57**, 1261-8 (2007).
125. Teichtahl, A.J. *et al.* The interaction between physical activity and amount of baseline knee cartilage *Rheumatology (Oxford)* **In press** (2016).
126. Dore, D.A. *et al.* The association between objectively measured physical activity and knee structural change using MRI. *Ann Rheum Dis* **72**, 1170-5 (2013).
127. Teichtahl, A.J. *et al.* Effect of long-term vigorous physical activity on healthy adult knee cartilage. *Med Sci Sports Exerc* **44**, 985-92 (2012).
128. Nicholls, A.S. *et al.* The association between hip morphology parameters and nineteen-year risk of end-stage osteoarthritis of the hip: a nested case-control study. *Arthritis Rheum* **63**, 3392-400 (2011).

129. Timmler, T., Wierusz-Kozlowska, M., Wozniak, W., Markuszewski, J. & Lempicki, A. Development and remodeling of the hip joint of preterm neonates in sonographic evaluation. *Ortop Traumatol Rehabil* **5**, 703-11 (2003).

130. Hussain, S.M. *et al.* Association of low birth weight and preterm birth with the incidence of knee and hip arthroplasty for osteoarthritis. *Arthritis Care Res (Hoboken)* **67**, 502-8 (2015).

131. Agricola, R. *et al.* Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). *Ann Rheum Dis* **72**, 918-23 (2013).

132. Siebenrock, K.A. *et al.* The cam-type deformity of the proximal femur arises in childhood in response to vigorous sporting activity. *Clin Orthop Relat Res* **469**, 3229-40 (2011).

133. Siebenrock, K.A., Kaschka, I., Frauchiger, L., Werlen, S. & Schwab, J.M. Prevalence of cam-type deformity and hip pain in elite ice hockey players before and after the end of growth. *Am J Sports Med* **41**, 2308-13 (2013).

134. Siebenrock, K.A., Behning, A., Mamisch, T.C. & Schwab, J.M. Growth plate alteration precedes cam-type deformity in elite basketball players. *Clin Orthop Relat Res* **471**, 1084-91 (2013).

135. Agricola, R. *et al.* A cam deformity is gradually acquired during skeletal maturation in adolescent and young male soccer players: a prospective study with minimum 2-year follow-up. *Am J Sports Med* **42**, 798-806 (2014).

136. Karlson, E.W. *et al.* Total hip replacement due to osteoarthritis: the importance of age, obesity, and other modifiable risk factors. *Am J Med.* **114**, 93-8. (2003).

137. Jensen, L.K. Hip osteoarthritis: influence of work with heavy lifting, climbing stairs or ladders, or combining kneeling/squatting with heavy lifting. *Occup Environ Med* **65**, 6-19 (2008).

138. Teichtahl, A.J. *et al.* Occupational risk factors for hip osteoarthritis are associated with early hip structural abnormalities: a 3.0 T magnetic resonance imaging study of community-based adults. *Arthritis Res Ther* **17**, 19 (2015).

139. NICE. Osteoarthritis Care and management in adults. http://guidance.nice.org.uk/cg177 (2014).

140. Hochberg, M.C. *et al.* American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* **64**, 465-74 (2012).

141. Fernandes, L. *et al.* EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* **72**, 1125-35 (2013).

142. Zhang, W. *et al.* EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. *Ann Rheum Dis* **69**, 483-9 (2010).

143. Zhang, W. *et al.* EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. *Ann Rheum Dis* **68**, 8-17 (2009).

144. McAlindon, T.E. *et al.* OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* **22**, 363-88 (2014).

145. Bruyere, O. *et al.* An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Semin Arthritis Rheum* **44**, 253-63 (2014).

146. Belo, J.N., Berger, M.Y., Reijman, M., Koes, B.W. & Bierma-Zeinstra, S.M. Prognostic factors of progression of osteoarthritis of the knee: a systematic review of observational studies. *Arthritis Rheum* **57**, 13-26 (2007).

147. Christensen, R., Bartels, E.M., Astrup, A. & Bliddal, H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* **66**, 433-9 (2007).

148. Fransen, M. *et al.* Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev* **1**, CD004376 (2015).

149. Fransen, M., McConnell, S., Hernandez-Molina, G. & Reichenbach, S. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev* **4**, CD007912 (2014).
150. Ruhdorfer, A., Wirth, W. & Eckstein, F. Longitudinal Change in Thigh Muscle Strength Prior to and Concurrent With Minimum Clinically Important Worsening or Improvement in Knee Function: Data From the Osteoarthritis Initiative. *Arthritis Rheumatol* **68**, 826-36 (2016).
151. Hunter, D.J. *et al.* The Intensive Diet and Exercise for Arthritis (IDEA) trial: 18-month radiographic and MRI outcomes. *Osteoarthritis Cartilage* **23**, 1090-8 (2015).
152. Messier, S.P. *et al.* Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. *JAMA* **310**, 1263-73 (2013).
153. Atukorala, I. *et al.* Is there a dose response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? *Arthritis Care Res (Hoboken)*, DOI: 10.1002/acr.22805 (2016).
154. Rannou, F. *et al.* Splint for base-of-thumb osteoarthritis: a randomized trial. *Ann Intern Med* **150**, 661-9 (2009).
155. Gomes Carreira, A.C., Jones, A. & Natour, J. Assessment of the effectiveness of a functional splint for osteoarthritis of the trapeziometacarpal joint on the dominant hand: a randomized controlled study. *J Rehabil Med* **42**, 469-74 (2010).
156. Jones, A. *et al.* Impact of cane use on pain, function, general health and energy expenditure during gait in patients with knee osteoarthritis: a randomised controlled trial. *Ann Rheum Dis* **71**, 172-9 (2012).
157. Callaghan, M.J. *et al.* A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. *Ann Rheum Dis* **74**, 1164-70 (2015).
158. Palmer, S. *et al.* Transcutaneous electrical nerve stimulation as an adjunct to education and exercise for knee osteoarthritis: a randomized controlled trial. *Arthritis Care Res (Hoboken)* **66**, 387-94 (2014).
159. Laufer, Y. & Dar, G. Effectiveness of thermal and athermal short-wave diathermy for the management of knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* **20**, 957-66 (2012).
160. Zhang, W. *et al.* OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* **18**, 476-99 (2010).
161. Machado, G.C. *et al.* Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ* **350**, h1225 (2015).
162. Roberts, E. *et al.* Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis* **75**, 552-9 (2016).
163. da Costa, B.R. *et al.* Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet*, DOI: 10.1016/S0140-6736(16)30002-2 (2016).
164. Singh, J.A., Noorbaloochi, S., MacDonald, R. & Maxwell, L.J. Chondroitin for osteoarthritis. *Cochrane Database Syst Rev* **1**, CD005614 (2015).
165. Towheed, T.E. *et al.* Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* **18**, CD002946 (2005).
166. Hochberg, M.C. *et al.* Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. *Ann Rheum Dis* **75**, 37-44 (2016).

167. Martel-Pelletier, J. *et al.* First-line analysis of the effects of treatment on progression of structural changes in knee osteoarthritis over 24 months: data from the osteoarthritis initiative progression cohort. *Ann Rheum Dis* **74**, 547-56 (2015).
168. Fransen, M. *et al.* Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. *Ann Rheum Dis* **74**, 851-8 (2015).
169. Rutjes, A.W. *et al.* Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med* **157**, 180-91 (2012).
170. Lewis, G.N., Rice, D.A., McNair, P.J. & Kluger, M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. *Br J Anaesth* **114**, 551-61 (2015).
171. Kahan, A., Uebelhart, D., De Vathaire, F., Delmas, P.D. & Reginster, J.Y. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* **60**, 524-33 (2009).
172. Reginster, J.Y. *et al.* Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* **357**, 251-6 (2001).
173. Wildi, L.M. *et al.* Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. *Ann Rheum Dis* **70**, 982-9 (2011).
174. Pelletier, J.P. *et al.* Disease-modifying effect of strontium ranelate in a subset of patients from the Phase III knee osteoarthritis study SEKOIA using quantitative MRI: reduction in bone marrow lesions protects against cartilage loss. *Ann Rheum Dis* **74**, 422-9 (2015).
175. Glyn-Jones, S. *et al.* Osteoarthritis. *Lancet* **386**, 376-87 (2015).
176. Woolf, A.D. & Pfleger, B. Burden of major musculoskeletal conditions. *Bull World Health Organ* **81**, 646-56 (2003).
177. Hiligsmann, M. *et al.* Health economics in the field of osteoarthritis: an expert's consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Semin Arthritis Rheum* **43**, 303-13 (2013).
178. Vos, T. *et al.* Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**, 2163-96 (2012).
179. Cross, M. *et al.* The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* **73**, 1323-30 (2014).
180. Litwic, A., Edwards, M.H., Dennison, E.M. & Cooper, C. Epidemiology and burden of osteoarthritis. *Br Med Bull* **105**, 185-99 (2013).
181. Palazzo, C., Ravaud, J.F., Papelard, A., Ravaud, P. & Poiraudeau, S. The burden of musculoskeletal conditions. *PLoS One* **9**, e90633 (2014).
182. Cooper, C. & Arden, N.K. Excess mortality in osteoarthritis. *BMJ* **342**, d1407 (2011).
183. Nuesch, E. *et al.* All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. *BMJ* **342**, d1165 (2011).
184. Hawker, G.A. *et al.* All-cause mortality and serious cardiovascular events in people with hip and knee osteoarthritis: a population based cohort study. *PLoS One* **9**, e91286 (2014).
185. Barbour, K.E. *et al.* Hip Osteoarthritis and the Risk of All-Cause and Disease-Specific Mortality in Older Women: A Population-Based Cohort Study. *Arthritis Rheumatol* **67**, 1798-805 (2015).
186. Uhlig, T., Slatkowsky-Christensen, B., Moe, R.H. & Kvien, T.K. The burden of osteoarthritis: The societal and the patient perspective. *Therapy* **7**, 605-619 (2010).
187. Hochberg, M.C. Mortality in osteoarthritis. *Clin Exp Rheumatol* **26**, S120-4 (2008).

188. Pelletier, J.-P. & Martel-Pelletier, J. The DMOAD dream: A generation later. *The Rheumatologist* **5**, 18-20 cont'd 52 (2011).
189. Martel-Pelletier, J., Wildi, L.M. & Pelletier, J.P. Future therapeutics for osteoarthritis. *Bone* **51**, 297-311 (2012).
190. Peterfy, C.G., Schneider, E. & Nevitt, M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. *Osteoarthritis Cartilage* **16**, 1433-41 (2008).
191. Ding, C. *et al.* Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. *Ann Rheum Dis* **67**, 1256-61 (2008).
192. Solomon, D.H. *et al.* The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med* **170**, 1968-76 (2010).
193. Cooper, C. *et al.* How to define responders in osteoarthritis. *Curr Med Res Opin* **29**, 719-29 (2013).
194. Arden, N. *et al.* Can We Identify Patients with High Risk of Osteoarthritis Progression Who Will Respond to Treatment? A Focus on Biomarkers and Frailty. *Drugs Aging* **32**, 525-35 (2015).
195. Roubille, C., Pelletier, J.P. & Martel-Pelletier, J. in Osteoarthritis: Pathogenesis, Diagnosis, Available Treatments, Drug Safety, Regenerative and Precision Medicine (eds. Kapoor, M. & Mahomed, N.N.) 191-210 (Springer International Publishing, Switzerland, 2015).
196. Berenbaum, F., Pelletier, J.P. & Burkhard, L. Osteoarthritis: The challenge of establishing a personalised treatment. *EMJ Rheumatol* **1**, 33-39 (2014).
197. Roubille, C., Pelletier, J.P. & Martel-Pelletier, J. New and emerging treatments for osteoarthritis management: will the dream come true with personalized medicine? *Expert Opin Pharmacother* **14**, 2059-77 (2013).
198. van der Esch, M. *et al.* Clinical phenotypes in patients with knee osteoarthritis: a study in the Amsterdam osteoarthritis cohort. *Osteoarthritis Cartilage* **23**, 544-9 (2015).
199. Conaghan, P.G., Hunter, D.J., Maillefert, J.F., Reichmann, W.M. & Losina, E. Summary and recommendations of the OARSI FDA osteoarthritis Assessment of Structural Change Working Group. *Osteoarthritis Cartilage* **19**, 606-10 (2011).
200. Poole, A.R. What type of cartilage repair are we attempting to attain? *J Bone Joint Surg Am* **85-A Suppl 2**, 40-4 (2003).
201. Otero, M., Loeser, R. & Goldring, M.B. Inflammation and osteoarthritis. *OARSI Primer*, http://primer.oarsi.org.
202. Barr A, Conaghan P.G. Osteoarthritis: recent advances in diagnosis and management. *Prescriber* **25**, 26-33 (2014).

Reference annotations

36. Heinegard, D. & Saxne, T. The role of the cartilage matrix in osteoarthritis. *Nat Rev Rheumatol* **7**, 50-6 (2011).
Comprehensive overview of the composition of articular cartilage and the molecular and cellular changes associated with osteoarthritis.

61. Burr, D.B. & Gallant, M.A. Bone remodelling in osteoarthritis. *Nat Rev Rheumatol* **8**, 665-73 (2012).
Overview of osteoarthritis bone pathology and the role of bone in osteoarthritis pathogenesis.

82. Liu-Bryan, R. & Terkeltaub, R. Emerging regulators of the inflammatory process in osteoarthritis. *Nat Rev Rheumatol* **11**, 35-44 (2015).
Overview of the molecular mechanisms involved in joint inflammation in osteoarthritis.

116. Teichtahl, A.J. *et al.* Vastus medialis fat infiltration - a modifiable determinant of knee cartilage loss. *Osteoarthritis Cartilage* **23**, 2150-7 (2015).
This paper shows that fat atrophy of the quadriceps, which can be modified, is associated with structural changes in knee cartilage. Intramuscular fat may be a therapeutic target for altering the natural history of knee osteoarthritis.

117. Raynauld, J.P. *et al.* Magnetic Resonance Imaging-Assessed Vastus Medialis Muscle Fat Content and Risk for Knee Osteoarthritis Progression: Relevance From a Clinical Trial. *Arthritis Care Res (Hoboken)* **67**, 1406-15 (2015).
In addition to showing that vastus medialis fat content is a strong predictor of cartilage volume loss, this study demonstrated that combining vastus medialis area and fat content, and body mass index identified patients at higher risk for osteoarthritis progression.

126. Dore, D.A. *et al.* The association between objectively measured physical activity and knee structural change using MRI. *Ann Rheum Dis* **72**, 1170-5 (2013).
These data demonstrate that the influence of physical activity on joint structure is dependent upon the underlying health of the knee joint.

152. Atukorala, I. *et al.* Is there a dose response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? *Arthritis Care Res (Hoboken)*, DOI: 10.1002/acr.22805 (2016).
This study highlights the importance of weight loss in the treatment of osteoarthritis by demonstrating a dose response effect between percentage weight loss and improvement of symptoms in a cohort of obese individuals with symptomatic knee osteoarthritis.

156. Callaghan, M.J. *et al.* A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. *Ann Rheum Dis* **74**, 1164-70 (2015).

This study identifies the efficacy of a knee brace in the treatment of patellofemoral osteoarthritis, where it conferred structural and symptomatic benefits by reducing the size of bone marrow lesions and knee pain.

[Referees: Please note that all figures will be redrawn before publication.]

FIGURE LEGENDS

Figure 1. Prevalence of osteoarthritis: Dutch population sample[26]. Age and sex-specific prevalence rates for radiographic osteoarthritis affecting the distal interphalangeal (DIP) joint, knee and hip in a large Dutch population sample.

Figure 2. Incidence of symptomatic osteoarthritis of the hand, knee and hip. Data from the Fallon Community Health Plan[29].

Figure 3. Histological cross section of a normal diarthrodial joint illustrating the major structural elements, including the articular cartilage (with chondrocytes), tidemark (separating the calcified and articular cartilage), calcified cartilage, and subchondral cortical and trabecular bone. Also illustrated are the organisation and composition of the articular cartilage extracellular matrix[36,200].

Figure 4. Histopathologic cross section of a joint with advanced osteoarthritic changes characterised by fissuring and fragmentation of the articular cartilage, chondrocyte proliferation and hypertrophy, duplication and advancement of the tidemark, expansion of the zone of calcified cartilage, thickening of the subchondral cortical plate and vascular invasion of the bone and calcified cartilage. Histology provided by Edward F. DiCarlo, MD, Pathology Department, Hospital for Special Surgery, New York, NY.

Figure 5. A) Osteocytes decrease sclerostin levels in response to increased mechanical loading. Sclerostin is an inhibitor of the Wnt pathway that regulates osteoblast differentiation. Decreased sclerostin results in increased Wnt signalling and enhanced osteoblast-mediated bone formation.

B) Osteocytes increase RANKL in response to unloading. RANKL induces osteoclast differentiation leading to increased bone resorption.

Figure 6. Cellular mechanisms of periarticular bone adaptation. In response to altered mechanical forces, periarticular bone alters its structural organisation and shape via cell-mediated processes of remodelling, modelling and endochondral ossification.

Figure 7. Representative synovial OA histopathology. Panel (a) depicts normal appearing synovial membrane with a thin lining layer and loose connective tissue subintimal layer. The section in panel (b) demonstrates synovial lining hyperplasia (arrow), villous hyperplasia (arrowhead), fibrosis (star) and perivascular mononuclear cell infiltrates (double-headed arrow). Panel (c) depicts the distribution of synovial macrophages (CD68+ cells) concentrated in the synovial lining layer and (d) scattered throughout the subintimal layer and the perivascular infiltrates. Panels (e) and (f) demonstrate that the majority of cells within the perivascular infiltrates express markers of (e) T (CD3+) and (f) B lymphocytes (CD20+). Reproduced from[76].

Figure 8. Model of cross-talk between cartilage and synovium in the pathogenesis of OA[201]. Products released from the cartilage matrix and/or the chondrocytes in response to adverse mechanical forces and systemic factors (e.g. obesity and adipokines) induce the release of products that deregulate chondrocyte function via paracrine and autocrine mechanisms. Catabolic enzymes released by the chondrocytes degrade the cartilage matrix releasing extracellular matrix (ECM) products that, along with the other proinflammatory chondrocyte derived-products, act on the synovium to induce inflammation and the release of proinflammatory products that feedback

on the chondrocytes to further deregulate their function.

Figure 9. A growing understanding of the complexity of risk factors for knee osteoarthritis.

Figure 10. Various pathways by which novel risk factors influence the pathogenesis of hip osteoarthritis.

Figure 11. OARSI Guidelines for the non-surgical management of knee osteoarthritis. Reproduced from[144].

New Figure A. Examples of knee and hand radiographic osteoarthritis. Note the presence of joint space narrowing and osteophytes in both radiographs and the presence of chondrocalcinosis in the knee which is commonly associated with osteoarthritis.

New Figure B. Knee MRI showing all the characteristic features of osteoarthritis on MRI on T2. (a) suprapatellar effusion; (b) patella cartilage defect; (c) bone marrow lesion; (d) large osteophyte; (e) Hoffa's synovitis; (f) anterior horn meniscal tear. Reproduced with permission from[102].

Table 1. Inflammatory mediators, catabolic factors and cell or matrix-derived products in the OA joint (synovium and chondrocyte)

Cytokines/Chemokines	Inflammatory Mediators	Matrix Degradation	Cell/Matrix Derived Products
IL-1	PGE_2	MMP-1	Alarmins (S100, etc.)
IL-6	NO	MMP-3	Fibronectin fragments
IL-15	ROS	MMP-13	HA fragments
OSM	Complement	Aggrecanase	Collagen fragments
TNF-α		(ADAMTS4, 5)	Proteoglycan fragments
Chemokines		Cathepsins	HMGB1

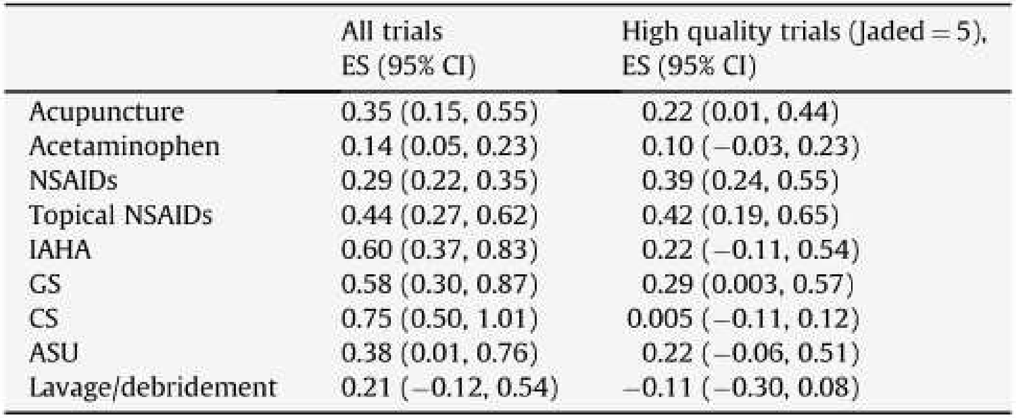
Abbreviations: IL, interleukin; PGE_2, prostaglandin E_2; MMP, matrix metalloproteinase; NO, nitric oxide; ROS, reactive oxygen species; HA, hyaluronic acid; OSM, oncostatin M; TNF, tumour necrosis factor; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; HMGB, high mobility group box.

Table 2. Summary of the latest evidence-based guidelines for OA treatments

Guideline Site of Osteoarthritis	NICE 2014 All sites	ESCEO 2014 Knee	OARSI 2014 Knee	OARSI 2014 Multi-joint	EULAR 2013 Knee and Hip	ACR 2012 Hand	ACR 2012 Knee	ACR 2012 Hip
Therapy								
Exercise / physiotherapy / water and land based	+	+	+	+	+	NE	+	+
Education, self-management	+	+	+	+	+	(+)	(+)	(+)
Weight loss in obesity	+	+	+	+	+	NE	+	+
Thermotherapy (e.g. hot packs/spa)	+	+	NR	(+)	NE	(+)	(+)	(+)
Acupuncture	-	+	NR	NR	NE	NE	(+)	NE
Transcutaneous electrical nerve stimulation	+	+	NR	-	NE	NE	(+)	NE
Aids, adaptations, braces, footwear (site specific)	+	(+)	(+)	(+)	+	(+)	(+)	(+)
Paracetamol	+	+	(+)	+	NE	NE	(+)	(+)
Topical NSAIDs	+	+	+	NR	NE	(+)	(+)	NR
Oral NSAIDs (lowest possible dose)	+	+	(+)	(+)	NE	(+)	(+)	(+)
Topical capsaicin	+*	(+)	(+)	NR	NE	(+)	-	NE
Opioids (for refractory pain)	(+)	+	NR	NR	NE	-	(+)	NR
Nutraceuticals -glucosamine and chondroitin sulfate	-	+	NR	NR	NE	NE	-	-
Duloxetine	NE	(+)	NR	+	NE	NE	(+)	NR
Risedronate	NE	NE	-	-	NE	NE	NE	NE
Strontium	-	NE	NE	NE	NE	NE	NE	NE
Intra-articular corticosteroids	+	(+)	(+)	+	NE	-	(+)	(+)
Intra-articular hyaluronans	-	(+)	NR	-	NE	-	(+)	NR
Surgery - Lavage/debridement	-$^{\#}$	-	NE	NE	NE	NE	NE	NE
Surgery - TJR / arthroplasty (site specific)	(+)	(+)	+	NE	NE	NE	NE	NE

+, treatment is unconditionally recommended; (+), treatment is conditionally recommended; -, treatment is not recommended; NE, treatment not evaluated; NR, no recommendation for treatment despite reviewing the evidence; *, excluding hip osteoarthritis; $^{\#}$, unless there is a clear history of mechanical knee locking. Abbreviations: NICE, National Institute for Health and Care Excellence[139]; ESCEO, European Society for Clinical and Economical Aspects of Osteoporosis and Osteoarthritis; OARSI, Osteoarthritis Research Society International; EULAR, European League Against Rheumatism; ACR, American College of Rheumatology; NSAID, non-steroidal anti-inflammatory drug; TJR, total joint replacement. This is not a head-to-head comparison of the guidelines but a summary of the recommendations. Each guideline addresses different anatomical sites. Table adapted from[202].

Table 3 Relationship between effect size for pain relief and quality of randomised controlled trial



	All trials ES (95% CI)	High quality trials (Jaded = 5), ES (95% CI)
Acupuncture	0.35 (0.15, 0.55)	0.22 (0.01, 0.44)
Acetaminophen	0.14 (0.05, 0.23)	0.10 (−0.03, 0.23)
NSAIDs	0.29 (0.22, 0.35)	0.39 (0.24, 0.55)
Topical NSAIDs	0.44 (0.27, 0.62)	0.42 (0.19, 0.65)
IAHA	0.60 (0.37, 0.83)	0.22 (−0.11, 0.54)
GS	0.58 (0.30, 0.87)	0.29 (0.003, 0.57)
CS	0.75 (0.50, 1.01)	0.005 (−0.11, 0.12)
ASU	0.38 (0.01, 0.76)	0.22 (−0.06, 0.51)
Lavage/debridement	0.21 (−0.12, 0.54)	−0.11 (−0.30, 0.08)

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; IAHA, intra-articular hyaluronic acid; GS, glucosamine; CS, chondroitin sulfate; ASU, avocado soybean unsaponifiables
Table reproduced from[160]