JPP JOURNAL OF Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY
JPP Journal of Pharmacy And Pharmacology
Review

Osteoarthritis of the knee and hip. Part I: aetiology and pathogenesis as a basis for pharmacotherapy

Aleem Adatia[a], K. D. Rainsford[b] and Walter F. Kean[a]

[a]Department of Medicine, McMaster University Faculty of Health Sciences, Hamilton, ON, Canada and [b]Biomedical Research Centre, Sheffield Hallam University, Sheffield, UK

Keywords
bone; cartilage; ibuprofen; inflammation; osteoarthritis

Correspondence
Walter F. Kean, #401, 1 Young Street, Hamilton, Ontario, Canada L8 1T8.
E-mail: keanmac@cogeco.ca

Received July 12, 2011
Accepted December 16, 2011

doi: 10.1111/j.2042-7158.2012.01458.x

Abstract

Objectives Osteoarthritis (OA) of the knee and hip is among the most frequent and debilitating arthritic conditions. Aside from surgical intervention in severe cases, conventional treatment involves relieving painful symptoms with non-steroidal anti-inflammatory drugs (NSAIDs), narcotic and non-narcotic (weak) analgesics and physical therapy. To obtain insight into the extent of pathological changes in hip and knee OA we reviewed current literature on the pathogenesis of this state as a basis for current pharmacotherapy options.

Key findings Key features of the pathological joint changes in OA include: cartilage destruction by pro-inflammatory cytokines, matrix metalloproteinases and prostaglandins, which promote a catabolic environment; subchondral bone remodelling and resorption; hypertrophic differentiation of chondrocytes; neovascularisation of synovial tissue; and focal calcification of joint cartilage. Despite the central involvement of hyaline cartilage in OA pathogenesis, the source of pain likely stems from the richly innervated synovium, subchondral bone and periosteum components of the joint. Tissue damage during joint degeneration generates nociceptive stimuli. The presence of inflammatory mediators, including bradykinin, prostaglandins and leukotrienes, lowers the threshold of the Aδ and C pain fibres, resulting in a heightened response to painful stimuli.

Summary It is our opinion that it is important to base and centre the management of OA patients on the severity of patient-important outcomes, rather than purely an assessment of damage to the joint. The joint damage, as interpreted from radiographs, is not necessarily representative of the symptoms experienced. The management of OA primarily comprises pharmacological therapy, surgical interventions and various non-pharmacological interventions.

Introduction

Osteoarthritis (OA) is the most common musculoskeletal joint disease worldwide, affecting individuals from all countries and races.[1–4] The most significant problem for OA patients is pain and discomfort, which can lead to additional problems such as limitations in function and altered social behaviour both at home and in the workplace.[1,2] It is also one of the oldest known diseases, having been noted in skeletons of dinosaurs, Egyptian mummies and human skeletons found in the UK.[3] Despite its prevalence throughout history, the aetiology is not yet fully understood. An exact definition of the disease has not been established due to its heterogeneous nature and diverse contributing factors.[1–5]

The treatment of OA involves multiple interventions, both pharmacological and non-pharmacological, according to the severity of joint destruction in this disease.[6,7] Non-steroidal anti-inflammatory drugs (NSAIDs) and non-narcotic and narcotic drugs constitute the mainstay of pain-relieving therapy in OA, although the efficacy of these drugs and their attendant adverse reactions vary considerably among these treatments.[6–8]

In this review we consider the factors implicated in the development and pathogenesis of OA focusing in particular on one of the most common sites of this condition, the knee, and using this understanding to establish a basis for current pharmacotherapy practices.

Aetiology and pathogenesis of osteoarthritis

OA is a disorder of diarthrodial (synovial) joints, characterized by degeneration and loss of articular cartilage in association with changes in the underlying subchondral bone and synovium.[1,4,5,7] It involves a series of destructive inflammatory processes and a complex interplay of factors accompanying the destruction of the joint's integrity and progression to joint dysfunction and pain.[5,6,7] OA can be sub-classified as either primary or secondary.[4,5,7] Primary or idiopathic OA refers to cases where the disease occurrence is not related to any prior condition or event affecting that joint, but which occur in definable patterns.[4] When the disease occurs in joints that have previously experienced trauma, pre-existing disease, or deformity, it is referred to as secondary OA. The common causes of secondary OA include fractures, congenital disorders and metabolic disorders; they are outlined in Table 1 from Buchanan and Kean[6] (as modified with details from Michael *et al*.[7]).

OA can occur in any diarthrodial joint, but is most commonly found in the hip, knee, facet joints of the spine, distal/proximal interphalangeal (DIP and PIP) joints of the hand and metacarpal trapezioscaphoid joints of the thumb base.[5] It is often the case that multiple joints are involved, although the condition can be limited to an individual joint.[1]

Epidemiological evidence of occurrence and impact of osteoarthritis

An examination of the worldwide epidemiology of OA reveals that it poses a pressing public health concern.[2,9–15] The prevalence and corresponding societal burden of OA is sizable, with the cost to developed countries thought to be trailing only that of cardiovascular disease.[2] Analyses solely of OA's socioeconomic data are limited, often clumped together with other arthritic conditions.

Table 1 Some causes of secondary osteoarthritis[5–7]

Congenital	Localized diseases (e.g. congenital hip dislocation, Legg-Calvė-Perthes disease, slipped femoral epiphysis). Bone dysplasias (e.g. multiple epiphyseal dysphasia, spindylo-epiphyseal dysplasia, malposition (varus/valgus))
Trauma	Both acute and chronic involving the joint or nearby bone causing malalignment
Metabolic	Ochronosis, haemochromatosis, Wilson's disease (hepato-lenticular degeneration), calcium pyrophosphate dihydrate disease (CPPD), rickets
Endocrine	Acromegaly, diabetes mellitus, obesity
Joint disease	Septic arthritis, rheumatoid arthritis, gout
Neurological	Charcot's arthropathy (tabes dorsales, diabetes, syringomyelia and Charcot-Marie-Tooth disease)
Vascular	Avascular necrosis
Bone disease	Paget's disease of bone (osteitis deformans)
Unknown	Kashin-Beck or Uror disease, Meseleni disease? Selenium deficiency.

The high prevalence of OA is confirmed in many recent studies in Western populations,[2,9–14] and is increasing in Asia.[15] Among the more recent extensive investigations to establish the incidence of OA in a national population is that provided by Kopec and co-workers,[16] who modelled the incidence of this condition in Canada using a Population Health microsimulation Model (PoHM) that they had developed. They used data based on physician reports and administrative data for the province of British Columbia, Canada and Quality of Life data based on Canadian national surveys. The incidence rates increased linearly in the 50–80 age range. In women the incidence was greater than in men. At 50 years of age the incidence per 1000 patient years ($10^{[3]}$ py) was 6.8 in men, while in women this was 8.2. By 80 years of age the incidence had risen to 23.8/$10^{[3]}$ py in men and 31.1/10^3 py in women.

Arthritis currently accounts for 2–3% of all disability, and this is expected to rise substantially.[2,8] Financial costs incurred by a country as a whole involve not only treating those suffering from arthritis, but also the disability and loss of work productivity related to disease problems. For example, costs of arthritis in the USA amount to almost $65 billion per year, with $15 billion in medical expenses and the remainder incurred from loss of work wages and other indirect costs.[17] In OA cases, it is the pain and the resulting limitation of activity that leads to work loss. Estimates place the total economic burden of arthritic diseases between 1 and 2.5% of gross national product in developed countries.[18] Although OA is generally not as individually disabling as rheumatoid arthritis, it is seven times more frequent in the population and thus contributes *en masse* to the bulk of the above-described socio-economic impact.[3] Estimates made by the World Health Organization (WHO) suggest that limitation of movement is experienced by 80% of people with OA, and that 25% are unable to carry out important daily activities.[18]

A major issue with OA of the hip and knee is that it is associated with high mortality (which increases with age), cardiovascular disease, diabetes mellitus and walking disability.[12,14] Obesity undoubtedly contributes markedly to both morbidity and mortality associated with OA[16,19,20] and contributes to deterioration in quality of life and marked increase in pain.[21]

The association with increase in inflammatory markers provides strong evidence that central obesity is the major component of what is described as a metabolic syndrome that contributes to OA.[21]

Risk factors

Attempts to determine the prevalence of OA are plagued with challenges due to the heterogeneity of the disease and sometimes also the difficulty in obtaining a clear diagnosis.[10,11,22,23] Notably, there is inconsistency between radiographic evidence of OA in patients and manifestation of symptoms especially with OA of the knee.[19–22] Early epidemiological studies noted that only 15% of patients with radiographic evidence of OA manifested corresponding symptoms.[10,24] Thus, prevalence determinations can vary greatly depending on diagnostic criteria and whether one is utilizing radiographic or symptomatic assessments. Lawrence *et al*.[11] estimated the prevalence of clinical (symptomatic) OA in the USA to be around 27 million adults. More recently it has been estimated from census-based data[25] that 13% of 14 338 292 adults aged 60–64 years old have radiographic and symptomatic evidence of knee OA. Among those surviving into the next decade, 20% will have symptomatic advanced or end-stage knee OA. Obese subjects will have a three-fold higher incidence of knee OA than the non-obese.[26] Use of magnetic resonance imaging (MRI) may increase the sensitivity of detection and assessment of progression of knee OA.[27]

Although OA is found in all age groups, older age is strongly correlated with occurrence of OA in all joints, and can be viewed as the predominant associated risk factor for the disease.[11,17] There is an exponential increase in the occurrence of severe OA after the age 50 years.[18] Estimates place the prevalence of OA at less than 5% of the 15–44-year-old bracket, 25–30% of 45–64-year-olds, and 65–90% of seniors, depending on the population of interest.[18] The strong age association has been partly attributed to biochemical changes in the matrix (containing proteoglycans and collagen fibres) of hyaline articular cartilage in synovial joints. Also, chondrocytes in older individuals are less able to produce proteoglycans to maintain the constitution of the cartilage matrix, making the joints more susceptible to OA.[3] The clear age association explains the increases in OA that have been seen, and will continue to be seen, due to an ageing population.[27]

Although all races are affected by OA, there are some notable variations in terms of prevalence and joint involvement among different races.[9,10,15] For example, hip OA is less frequent in the Chinese population; it is postulated that squatting practices confer a protective effect on the hip.[2] Most studies show that obesity is a considerable risk factor for OA in Asian populations and since obesity is increasing in this group it is apparent that OA is also becoming more prevalent along with aging of the population.[6,15] OA is also prevalent in rural Asian communities, associated with heavy physical occupational activity.[2] It is suggested that region-specific identification of the prevalence of OA will inform cost-effective measures in these populations in the future.[2] Cigarette smoking, which is increasingly prevalent in emerging economies, is also known to be associated, especially in men, with more severe knee pain and greater cartilage loss.[28]

Table 2 Endogenous and exogenous risk factors for osteoarthritis of the knee

Endogenous	Exogenous
Age: advancing age affect of both sexes altered locomotor (sterognostic) control of opposing muscle groups	Macrotrauma and repetitive loading repetitive microtrauma
Sex: females more prone to develop Heberden's nodes and, if obese, knee OA	Overweight (BMI > 30)
Heredity: Heberden's nodes inherited as autosomal trait. Genetically determined metabolic disorders (e.g. ochronosis and Ehler-Danlos syndrome) predispose to OA	
Ethnic origins: more common in persons of European descent. Less common in Asians. Climatic changes. Post-menopausal changes	Resective joint surgery

Modified from: Buchanan and Kean[2] and Michael *et al*.[7]

Obesity is also correlated with disease in the hand,[29] but no consistent association between obesity and hip-joint involvement has been identified.[2,3,10] High bone density is a predisposing factor for OA, while osteoporosis (low bone density) is thought to be protective of OA. These and other risk factors, including trauma, occupation, genetics and diet, are thoroughly reviewed by Buchanan and Kean.[2]

A summary of the endogenous and exogenous risk factors implicated in knee OA is shown in Table 2.[2,7]

Although early studies by Roberts and Burch in 1966[9] indicated that OA affects men and women equally, there have been increasing reports indicating that the burden of the disease is generally weighted more heavily on females.[16,27] It is clear that knee OA and hand OA (manifesting as Heberden's nodes) are more common in females but it is also noted that forms such as hip and spine OA tend to occur more often in males.[3] For example, women have a 37% greater risk of having knee OA than males, and this disparity increases for women over the age of 55.[14,16,27]

Genetic factors

These are amongst the most important of the endogenous factors implicated in predisposing individuals to OA.[7,30] Recent studies have shown that: (1) in female twins genetic factors play a major role in OA of the knee and hip; (2) in only a few rare cases is a single gene implicated; (3) it is most likely that the development and progression of OA is due to

interactions between multiple genes, including those controlling growth and differentiation, specific disease factors controlling joint erosion or destruction and inflammation, including nociception.[7,31,32] From these studies[30,31] it has been established that there is a 300-kilobase region in chromosome 7q22 associated with susceptibility to risk of OA. Moreover, these studies have identified genetic variants controlling: (1) production of molecules including growth and differentiation factor 5 (GDF5), which regulates signalling pathways; (2) production of extracellular matrix molecules (e.g. DVWA); (3) prostaglandin metabolism.[31]

Genetic association studies have also identified single nucleotide polymorphisms (SNP) (rs912428), among them a C/T transition in the LRCHI gene (which encodes for leucine-rich repeats and calponin homology domain containing protein 1) located in intron 1 of chromosome 13q14.[33] Other polymorphisms, including the rs143383 of the *GDF5* gene (which encodes growth differentiation factor 5) and rs7775 and rs288326 polymorphisms of the *FRZB* (which encodes the frizzled-related protein gene responsible for development and maintenance of bone and cartilage and is a key constituent in the Wnt signalling pathway that influences chondrocyte differentiation and cartilage growth), have been investigated but only the *GDF5* rs143383 polymorphisms have yet been implicated in OA.[34]

More recently, Waarsing and co-authors[35] have tried to identify OA susceptibility genes in relation to non-optimal geometry as a risk factor for OA of the hip. They took data on 190 sibling pairs and two trios of Dutch ancestry that had symptomatic OA and quantified radiographs according to different shape aspects of the hip, which they termed 'modes'. Each mode represented a specific pattern of variation in shape of the hip joints observed radiographically. The shape modes were then related to the SNP's of key genes that have been associated with skeletal development, and which have been identified with the OA susceptibility genes, *GDFS, FRZB* and *DI02* The results showed that 4 carrier status of *DI02* rs12885330 and OA hip characteristics for one of the modes of non-optimal shape. This suggests that the carriers of this gene SNP have increased vulnerability of cartilage to non-optimal shape. Two other shape modes were associated with 2 gene SNP's, *DI02* rs12885300 and *GDF5* rs143383 but these were not associated with characteristics of OA. These shape characteristics represented features of hip morphology and acetabular geometry.

Although more detailed genetic analysis is still required for hip OA, these studies give some insight into the importance of intrinsic morphological characteristics of hip joints and predisposition to OA. While, as previously noted,[31] there are growth and differentiation genetic variants associated with knee or hip OA, further discrimination and determination of these in relation to joint morphology along the lines of the study by Waarsing *et al*.[34] may prove important in understanding OA.

A prediction model has been developed by Takahashi *et al*.[36] based on a combination of genetic and clinical data in 2158 Japanese subjects of whom 933 had OA. As previously identified, the susceptibility gene *GDF5* as well as the asporin gene, *ASPN*, and a double version of von Willebrand factor A gene, *DVWA*, associated with OA were analysed and were not found to have good predictability. However, incorporation of clinical data improved the associations appreciably, especially when rigorous age adjustment was employed.

It is becoming recognized that heterogeneity in symptoms and radiographic classification of OA limit the identification of phenotypes. Recently a large international consortium (Translational Research in Europe Applied Technologies for OsteoArthritis (TREAT-OA)) has made recommendations for standardization and phenotypic descriptions for genetic analysis.[37] These form part of the overall objectives of TREAT-OA to identify risks for OA and new therapeutic targets.[37] Using these criteria the consortium identified the principal chromosome 7q22 associated with knee and hand OA.[30] Also, the same consortium identified a variant, (rs4140564) on chromosome 1, coding for the prostaglandin endoperoxide synthase-2 gene (COX-2), as being associated with knee OA.[38] This is of particular significance in view of prostaglandins being central to pain and inflammation in OA. In contrast, another inflammatory mediator system, in this case incorporating genes involved in the production and actions of interleukin 1 (IL-1), indicated that genetic variation in the genes controlling IL-1 are not associated with prevalence of knee or hip OA.[39] However, the interleukin receptor antagonist gene IL1RN might have a role in influencing the severity of knee OA.[39]

In a search for biomarkers based on genome-wide linkage studies, Chen and co-workers[40] showed that serum concentrations of the N-propeptide of type IIA collagen (PIIANP; chromosome 8q23.20), hyaluronan (HA; chromosome 6q16.3), cartilage oligomeric matrix protein (COMP; chromosome 8q11.1) and type Ii collagen neoepitope (C2C; chromosome 5q31.2) all had substantial heritable components (with logarith (base 10) of DODS scores of 2–4.3). These data are of particular interest since they imply that genetic variants of these genes, which are central to collagen, hyaluronan and cartilage growth, are potentially related to the occurrence of OA.

Another functional approach to understanding the genetics of knee OA has been observed in Chinese patients with inherited primary OA of the knee, (Kashin-Beck disease (KBD)).[41] This condition is characterized by multiple focal areas of chondronecrosis in mature chondrocytes of the growth plate and articular cartilage, and is frequently associated with selenium deficiency, mycotoxin-producing fungi or high humic-acid levels in drinking water.[41] Using an Agilent whole genome RT-PCR oligonucleotide micro array of RNA

from KBD and OA articular cartilage it was found that there was a two-fold higher differential expression (increased or decreased) in KBD compared with OA samples in some 6000 or more transcripts. The genes associated with chondrocyte matrix metabolism, cartilage degeneration and induction of apoptosis were all found to be implicated in KBD.

Cellular and molecular pathogenesis of osteoarthritis

There are numerous contributing mechanisms and a complex interrelated series of biochemical, mechanical and immunological events that give rise to the changes in articular cartilage (and the synovial joint as a whole) seen in OA. To date no single causative factor for OA joint damage has been identified and current views favour multiple causative factors (Table 2).

Joint structure related to changes in osteoarthritis

A brief overview of synovial joint structure may be helpful. In the synovial joints of healthy individuals, hyaline cartilage is present as a thin layer covering the articulating surfaces of the joint; it rests upon the subchondral bone, much like a covering material.[1] The cartilage serves to decrease friction and also distributes the force exerted by loads evenly onto the underlying bone; the cartilage itself is too thin to accept the load.[1,5] Cartilage cells, the chondrocytes, produce the elements of the extracellular matrix which include proteoglycans and collagen fibres (mainly type II). Collagen gives the cartilage tensile strength, and proteoglycan aggregates (called aggrecans) confer compressive strength. Glycosaminoglycans (including keratin sulfate) are bound to a protein core to form these aggrecans. The proteoglycan aggrecans are attached to hyaluronate via link protein to give a structural appearance of a test-tube brush in the matrix. Proteoglycan aggrecans bind lots of water and give hyaline cartilage a plentiful and hydrated matrix. Early in OA, there is a noted increase in the water content of hyaline cartilage accompanied by corresponding decreases in proteoglycan concentration, length and aggregation. The increased water content and proteoglycan changes decrease cartilage stiffness and give rise to fibrillation (rough appearance) of the cartilage surface. Severe fibrillation leads to formation of deep clefts that cannot be repaired despite the reparative efforts of chondrocytes, and cartilage proceeds to erode. Along with the cartilage damage, there are concurrent morphological changes in subchondral bone. Also seen is the formation of subarticular cysts (geodes) in the subchondral bone as synovial fluid infiltrates. Flattening of bone due to pressure, leads to the development of bony projections, known as osteophytes, in non-pressure areas of the joint. Osteophytes are characteristic features of OA and are easily identified in radiographs (Figure 1). Additionally, trabecular microfractures are seen in the subchondral bone and these are associated with the overlying cartilage damage.[42,43] Clinically, subchondral bone is frequently tender, especially in the knee, probably as a result of microfracture.[44] It has been previously identified that where the bone is tender, there is an increased uptake on isotope 99mTc scans.[5] This is identified from MRI studies as bone marrow oedema in the tibia and is predictive of OA.[45]

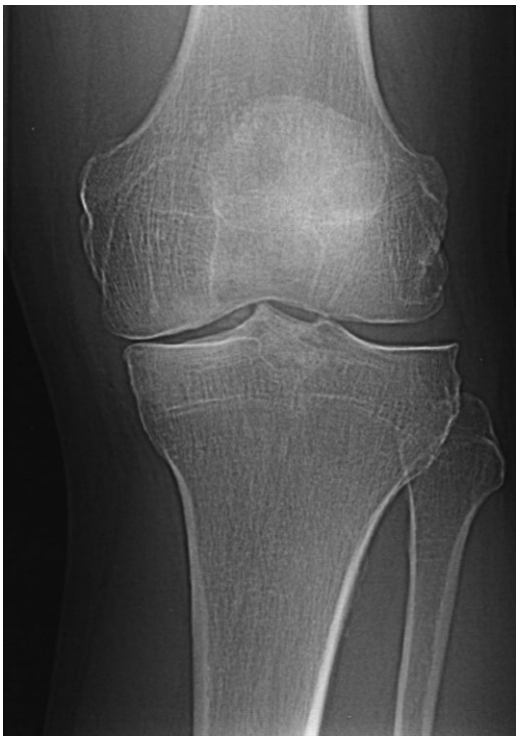

Figure 1 Osteophytes (bony spurs) and cartilage degradation in the tibiofemoral joint (right) gives rise to malalignment, pain and reduced physical function.[1]

In many cases of the disease, the debris from cartilage degradation is released into the synovial fluid and gives rise to synovitis. The synovial inflammation is viewed as a concomitant event contributing to the pathogenesis, and is due to the cartilage breakdown products (e.g. proteoglycan link protein) with immune-stimulating properties (Figure 2).[7,46]

Cytokines and other inflammatory mediators are first produced by the synovium where the inflammatory reaction is taking place, and then act on the chondrocytes.[47] The activated chondrocytes go on to produce a number of different cytokines and factors, such as tumour necrosis factor-α (TNFα), interleukin1β (IL-1β), nitric oxide (NO) and prostaglandins, that promote the catabolic environment in the cartilage and the ensuing structural changes.[46] Matrix

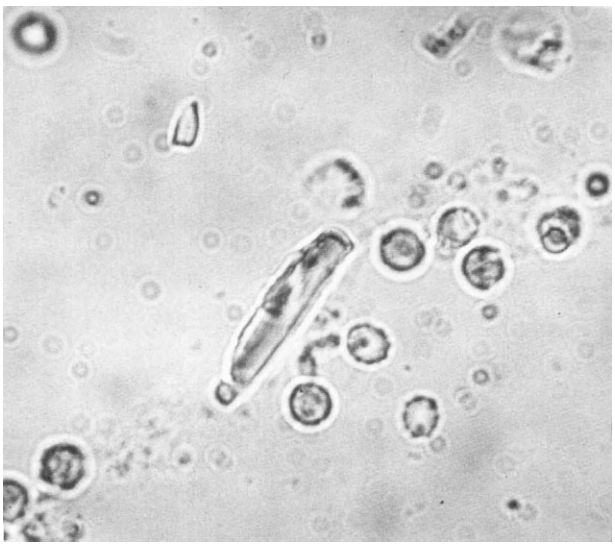

Figure 2 Cartilage breakdown products and debris with immune-stimulating properties may give rise to detritus synovitis, inflammation of the synovium.[6]

metalloproteinases (MMPs) have been shown to play a role in structural changes of cartilage early in the pathogenic process. These are produced by activated chondrocytes of osteoarthritic joints and include the protease aggrecanase, which cleaves proteoglycans. Collagenase is another potent MMP that cleaves collagen fibres, thereby breaking down the cartilage matrix.[46]

Despite the central role of hyaline cartilage in OA pathogenesis, it is an unlikely source of pain since it lacks innervation. Other components of the joint, such as the subchondral bone, synovium (which undergoes inflammation) and periosteum, are all richly innervated. C nerve fibres are unmyelinated and carry information to the central nervous system about diffuse, non-localized, burning pain. Aδ fibres carry information about sharp pain. Tissue damage during joint degeneration generates nociceptive stimuli that are carried by these afferents to the dorsal horn of the spinal cord and are perceived as pain by the brain. The inflammatory mediators produced by synovium and chondrocytes are able to lower the threshold of the Aδ and C fibres, resulting in an increase in their firing rate in response to painful stimuli. These mediators include bradykinin, prostaglandins and leukotrienes.[1,5,46]

Key features of the pathophysiology of joint changes in OA are: (1) cartilage destruction principally by pro-inflammatory cytokines, IL-1β and TNFα[47,48] generated by inflamed synovium and invading leucocytes, which cause release of matrix metalloproteinases (MMPs) from both synovium and cartilage; (2) subchondral bone remodelling and resorption of bone mediated by catabolic molecular pathways (e.g. receptor activator of nuclear factor-kappa B (NFkB) (RANK) and its ligand RANK-L, cathepsin K), as well as anabolic signalling (e.g. Wnt and fibroblast growth factor (FGF)-18) in new bone modelling;[49,50] (3) hypertropic differentiation of chondrocytes;[51] (4) neovascularization of synovial tissue;[51] (5) focal calcification of joint cartilage;[51] (6) production of mesenchymal stem cells as part of the homoeostatic compensatory mechanisms involved in regeneration.[52]

Recently, there has also been much interest in: (1) the molecular mechanisms underlying cartilage remodelling;[53] (2) the role of infrapatellar fat as a major source of pro-inflammatory cytokines, vascular sources of inflammatory cytokines, sensory nerve derived substance P and leptin, which all contribute to synovial inflammation, articular cartilage degeneration and osteophytosis;[54] (3) the impact of reduced muscle strength adjacent to OA knee joints resulting from increased pro-inflammatory cytokine expression in the vastus lateralis muscle along with expression of atrophy related genes;[55] (4) the increasing recognition of hypoxia-inducible factor-2α (HIF-2α) arising from mechanical loading or inflammatory changes mediated via NFkB signalling along with HIF-1α from hypoxia, which may represent key upstream initiating stimulatory pathways affecting cartilage homoeostasis and development of OA;[56,57] (5) the major role played by MMP-13 (collagenase-3) but with evidence for limited effectiveness of inhibitors of this enzyme;[57] (6) the discoid Denman receptor-2, syndecan-4, transforming growth factor-β and alarmins (myeloid related proteins 8 and 9) as regulators of chondrocyte degradative events;[57] (7) bone morphogenic proteins as regulators of chondrocyte differentiation and matrix remodelling;[58] (8) mitogen-activated protein kinases (MAPKs) as key regulators of cartilage proteoglycan degradation end products (AGEPs) and their receptors (RAGEs), which are produced or activated, respectively, in diabetes mellitus and most arthritides as initiators of pro-inflammatory changes, cell cycle arrest and osteoclastogenesis;[59,60] (9) the events involved in initiation of apoptosis in chondrocytes, which is largely driven by pro-inflammatory cytokines (e.g. TNFα).[61]

In the light of the plethora of molecular and cellular pathways in the pathogenesis of OA it is not surprising that there have been virtually no effective agents developed for arresting or reversing the joint destruction in this condition although there have been some encouraging developments.[6,49,51,52,57,61] Despite the application of anti-IL1 or anti-TNFα biologicals it is disappointing that these highly specific agents targeting 'upstream' inflammatory mediators have not realized their therapeutic potential.[61]

Responses to pharmacotherapy

Several groups of experts, using evidence-based medicine techniques, have developed proposals or 'guidelines' for the

management of hip or knee OA.[62–64] Thus there is a range of treatment modalities used in the management of OA. It is important to note that there is not a universal agreement on how to best treat hip and knee OA, although major international collaborative efforts have attempted to inform best practice on the basis of systematic reviews of published clinical trials. Among these is the initiative by the Osteoarthritis Research Society International (OARSI), whose recent recommendations represent the best comprehensive of available consensus information to date.[62–64]

This consensus report reviews available data on pharmacological, non-pharmacological and surgical treatments.[62–68] A popular view is that treatment of OA centres on both non-pharmacological treatments (exercises, education/information/self management, weight reduction, electromagnetic or ultrasound and other physical therapies) together with pharmacological treatments. Surgical treatment, largely consisting of arthroplasty of the hip and knees, can significantly improve pain and functionality in some OA patients.[2] About 90% of hip and knee replacements are for cases of OA[8], and it has been estimated that half of all hip OA patients referred to hospital clinics have symptoms that are severe enough to warrant hip-replacement surgery.[2] Pharmacological intervention is the most widely used form of treatment and involves the use of the simple analgesics such as paracetamol (acetaminophen) along with NSAIDs. There has been much debate about whether paracetamol or NSAIDs should be used as 'first-line' agents,[2,52–64] although paracetamol at up to 4 g/day has received wide advocacy. The recent OARSI (2010) review (along with European League against Rheumatism (EULAR), the UK National Institute for Clinical Excellence (NICE) and the American Society of Orthopedic Surgeons (AAOS) guidelines) recommended paracetamol 4 g/day for OA of the hip or knee and the strength of recommendation from OARSI is high, despite uncertainties about the long-term efficacy and safety of this drug.[64] This is a bizarre conclusion in view of the weight of evidence from OARSI analyses in which the cumulative meta-analysis suggests that the pain relief is small, particularly in comparison with that obtained using NSAIDs. Furthermore, paracetamol has no significant effect on stiffness or physical function in symptomatic knee OA.[64] What is of concern is that recent evidence suggests that far from having low gastrointestinal risk (especially compared with that from NSAIDs), paracetamol >3 g/day has appreciable upper gastrointestinal side effects (risk of hospitalization from perforation, ulceration or bleedings (PUBs)).[65] There is also evidence for mild loss of renal function in women following long-term consumption and decline in glomerular filtration rate.[66] Moreover, the incidence of hypertension in men[67] and cardiovascular conditions[68] associated with paracetamol is of concern. The recent advisory committee recommendations of the US Food and Drug Administration (FDA) indicate that the adult daily dose should be less than 4 g/day paracetamol and that over-the-counter preparations of this drug should be limited to 650 mg per unit dose because of concern about hepatotoxicity from paracetamol.[69] These concerns, as well as OARSI recommendations,[62–64] have therefore shifted the balance of evidence in favour of NSAIDs as first-line agents for hip and knee OA.[64,70] As ibuprofen is recognized as having the lowest risks for gastrointestinal and hepato-renal adverse events among the NSAIDs and is a widely used over-the-counter treatment for OA, we review elsewhere in this Journal, clinical evidence for efficacy and major adverse events.

Some authors (e.g. Herontin and Chevalier[71]) have found the 'expert guidelines' (e.g. those from the OARSI[62–64]) are not useful. The OARSI group has developed 25 guidelines, including 8 for pharmacology modalities, 12 for non-pharmacology modalities and 5 for surgery modalities.[62–64] Herontin and Chevalier[71] have stated that the usefulness of the guidelines in daily practice is very low, and the barriers for the guidelines' implementation are: the lack of interest of practitioners; the lack of scientific advances in OA diagnosis and treatments; and the low applicability of these guidelines in daily practice.

Conclusions

It is our opinion that it is important to base and centre the management of OA patients on the severity of patient-important outcomes, rather than purely an assessment of damage to the joint. The joint damage, as interpreted from radiographs, is not necessarily representative of the symptoms experienced. The management of OA primarily comprises pharmacological therapy, surgical interventions and various non-pharmacological interventions. The next paper in this set outlines the pharmacology and clinical aspects of the use of ibuprofen, one of the most commonly used NSAIDs, in OA of knees and hips.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This review received no grants from any funding agency in the public, commercial or nor-for-profit sectors.

References

1. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005; 365: 965–973.
2. Buchanan WW, Kean WF. Osteoarthritis I: epidemiological risk factors and historical considerations. *Inflammopharmacology* 2002; 10: 5–21.
3. Buchanan WW *et al*. History and current status of osteoarthritis in the population. *Inflammopharmacology* 2003; 11: 301–316.
4. Altman RD. Classification of disease: osteoarthritis. *Semin Arthritis Rheum* 1991; 20(S2): 40–47.
5. Buchanan WW, Kean WF. Osteoarthritis II: pathology and pathogenesis. *Inflammopharmacology* 2002; 10: 23–52.
6. Buchanan WW, Kean WF. Osteoarthritis IV: clinical therapeutic trials and treatment. *Inflammopharmacology* 2002; 10: 75–149.
7. Michael JW *et al*. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. *Dtsch Arztebl Int* 2010; 107: 152–162. [Erratum ibid, p. 292].
8. Hungin APS, Kean WF. Nonsteroidal anti-inflammatory drugs: overused or underused in osteoarthritis? *Am J Med* 2001; 110: 8S–11S.
9. Roberts J, Burch TJ. Prevalence of osteoarthritis in adults by age, sex, race and geographic area, United States 1960–1962. *National Center for Health Statistics: Vital and Health Statistics: Data from the National Health Survey*. Washington DC, US Government Printing Office, US Public Health Service Publication, 1000, Series 11, No. 15, 1966.
10. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Rheum Dis Clin North Am* 2008; 34: 515–529.
11. Lawrence RC *et al*.; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008; 58: 26–35.
12. Mendel OI *et al*. Osteoarthritis and vascular diseases in elderly patients: clinical and pathogenic interrelationships. *Adv Gerontol* 2010; 23: 304–313.
13. Forestier R *et al*. Prevalence of generalized osteoarthritis in a population with knee osteoarthritis. *Joint Bone Spine* 2011; 78: 275–278.
14. Nüesch E *et al*. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. *BMJ* 2011; 342: d1165.
15. Fransen M *et al*. The epidemiology of osteoarthritis in Asia. *Int J Rheum Dis* 2011; 14: 113–121.
16. Kopec JA *et al*. Development of a population-based microsimulation model of osteoarthritis in Canada. *Osteoarthritis Cartilage* 2010; 18: 303–311.
17. Hunter DJ *et al*. The symptoms of osteoarthritis and the genesis of pain. *Med Clin North Am* 2009; 93: 83–100.
18. Buckwalter JA, Martin JA. Osteoarthritis. *Adv Drug Deliv Rev* 2006; 58: 150–167.
19. Losina E *et al*. Impact of obesity and knee osteoarthritis on morbidity in older Americans. *Ann Intern Med* 2011; 154: 217–226.
20. Denisov LN *et al*. Role of obesity in the development of osteoarthritis and concomitant diseases. *Ter Arkh* 2010; 82: 34–37.
21. Ray L *et al*. Mechanisms of association between obesity and chronic pain in the elderly. *Pain* 2011; 152: 53–59.
22. Lawrence JS *et al*. Osteoarthritis prevalence in the population and relationship between symptoms and x-ray changes. *Ann Rheum Dis* 1966; 25: 1–24.
23. Duncan R *et al*. Symptoms and radiographic osteoarthritis: not as discordinant as they are made out to be? *Ann Rheum Dis* 2007; 66: 86–91.
24. Cooper C *et al*. Risk factors for the incidence and progression of radiographic knee osteoarthritis. *Arthritis Rheum* 2000; 43: 995–1000.
25. Cibere J *et al*. Association of clinical findings with pre-radiographic and radiographic knee osteoarthritis in a population-based study. *Arthritis Care Res* 2010; 62: 1691–1698.
26. Gibson K *et al*. Measurement of varus/valgus alignment in obese individuals with knee osteoarthritis. *Arthritis Care Res* 2010; 62: 690–696.
27. Holt HL *et al*. Forecasting the burden of advanced knee osteoarthritis over a 10-year period in a cohort of 60–64 year-old US adults. *Osteoarthritis Cartilage* 2011; 19: 44–50.
28. Amin S *et al*. Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. *Ann Rheum Dis* 2007; 66: 18–22.
29. Kellgren JH, Lawrence JS. Osteoarthritis and disk degeneration in an urban population. *Ann Rheum Dis* 1958; 17: 388–397.
30. Kerkhof HJ *et al*. A genome-wide association study identifies an osteoarthritis susceptibility locus on chromosome 7q22. *Arthritis Rheum* 2010; 62: 499–510.
31. Valdes AM, Spector TD. Genetic epidemiology of hip and knee osteoarthritis. *Nat Rev Rheumatol* 2011; 7: 23–32.
32. Kean WF *et al*. Women with pain due to osteoarthritis: the efficacy and safety of a once-daily formulation of tramadol. *Pain Med* 2009; 10: 1001–1011.
33. Snelling S *et al*. Genetic association analysis of *LRCH1* as an osteoarthritis susceptibility locus. *Rheumatol* 2007; 46: 250–252.
34. Evangelou E *et al*. Large-scale analysis of association between GDF5 and FRZB variants and osteoarthritis of the hip, knee, and hand. *Arthritis Rheum* 2009; 60: 1710–1721.
35. Waarsing JH *et al*. Osteoarthritis susceptibility genes influence the association between hip morphology and osteoarthritis. *Arthritis Rheum* 2011; 63: 1349–1354.
36. Takahashi H *et al*. Prediction model for knee osteoarthritis based on genetic and clinical information. *Arthritis Res Ther* 2010; 12: R187.
37. Kerkhof HJ *et al*. Recommendations for standardization and phenotype definitions in genetic studies of osteoarthritis: the TREAT-OA consortium. *Osteoarthritis Cartilage* 2011; 19: 254–264.
38. Valdes AM *et al*. Genome-wide association scan identifies a prostaglandin-endoperoxide synthase-2 variant involved in risk of knee osteoarthritis.

Am J Hum Genet 2008; 82: 1231–1240.
39. Kerkhof HJ *et al.* Large-scale meta-analysis of interleukin-1 beta and interleukin-1 receptor antagonist polymorphisms on risk of radiographic hip and knee osteoarthritis and severity of knee osteoarthritis. *Osteoarthritis Cartilage* 2011; 19: 265–271.
40. Chen HC *et al.* Genome-wide linkage analysis of quantitative biomarker traits of osteoarthritis in a large, multigenerational extended family. *Arthritis Rheum* 2010; 62: 781–790.
41. Duan C *et al.* Comparative analysis of gene expression profiles between primary knee osteoarthritis and an osteoarthritis endemic to Northwestern China, Kashin-Beck disease. *Arthritis Rheum* 2010; 62: 771–780.
42. Radin ER. Mechanical aspects of osteoarthritis. *Bull Rheum Dis* 1976; 23: 862–865.
43. Radin ER, Rose RM. Role of subchondral bone in the initiating and progression of cartilage damage. *Clin Orthop* 1986; 213: 34–40.
44. Wood DJ *et al.* Synthesis of alpha-1-antitrypsin by human articular chondrocytes. *Trans Orthop Res Soc* 1990; 15: 814–815.
45. Koster IM *et al.* Predictive factors for new onset or progression of knee osteoarthritis one year after trauma: MRI follow-up in general practice. *Eur Radiol* 2011; 21: 1509–1516. [Epub ahead of print].
46. Pelletier JP *et al.* Osteoarthritis, an Inflammatory Disease. *Arthritis Rheum* 2001; 44: 1237–1247.
47. Kapoor M *et al.* Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011; 7: 33–42.
48. Schroeppel JP *et al.* Molecular regulation of articular chondrocyte function and its significance in osteoarthritis. *Histol Histopathol* 2011; 26: 377–394.
49. Beyer C, Schett G. Pharmacotherapy: concept of pathogenesis and emerging treatments. Novel targets in bone and cartilage. *Best Pract Res Clin Rheumatol* 2010; 24: 489–496.
50. Tat SK *et al.* Modulation of OPG, RANK and RANKL by human chondrocytes and their implication during osteoarthritis. *Rheumatol* 2009; 48: 1482–1490.
51. Dreier R. Hypertrophic differentiation of chondrocytes in osteoarthritis: the development aspect of degenerative joint disorders. *Arthritis Res Ther* 2010; 12: 216.
52. Coleman CM *et al.* Mesenchymal stem cells and osteoarthritis: remedy or accomplice? *Hum Gene Ther* 2010; 21: 1239–1250.
53. Bertrand J *et al.* Molecular mechanisms of cartilage remodelling in osteoarthritis. *Int J Biochem Cell Biol* 2010; 42: 1594–1601.
54. Clockaerts S *et al.* The infrapatellar fat pad should be considered as an active osteoarthritic joint tissue: a narrative review. *Osteoarthritis Cartilage* 2010; 18: 876–882.
55. Levinger I *et al.* Increased inflammatory cytokine expression in the vastus lateralis of patients with knee osteoarthritis. *Arthritis Rheum* 2011; 63: 1343–1348.
56. Saito T, Kawaguchi H. HIF-2α as a possible therapeutic target of osteoarthritis. *Osteoarthritis Cartilage* 2010; 18: 1552–1556.
57. van den Berg WB. Osteoarthritis year 2010 in review: pathomechanisms. *Osteoarthritis Cartilage* 2011; 19: 338–341.
58. van der Kraan PM *et al.* Bone morphogenic proteins and articular cartilage to serve and protect or a wolf in sheep's clothing? *Osteoarthritis Cartilage* 2010; 18: 735–741.
59. Sondergaard B-C *et al.* MAPKS are essential upstream signalling pathways in proteolytic cartilage degradation – divergence in pathways leading to aggrecanase and MMP-mediated articular cartilage degradation. *Osteoarthritis Cartilage* 2010; 18: 279–288.
60. Franke S *et al.* Advanced glycation end products induce cell cycle arrest proinflammatory changes in osteoarthritis fibroblast-like synovial cells. *Arthritis Res Ther* 2009; 11: R136.
61. Kühn K *et al.* Cell death in cartilage. *Osteoarthritis Cartilage* 2004; 12: 1–16.
62. Zhang W *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007; 15: 981–1000.
63. Zhang W *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008; 16: 137–162.
64. 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* 2010; 18: 476–499.
65. Rahme E *et al.* Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. *Am J Gastroenterol* 2008; 103: 872–882.
66. Curhan GC *et al.* Lifetime nonnarcotic analgesic use and decline in renal function in women. *Arch Intern Med* 2004; 164: 1519–1524.
67. Forman JP *et al.* Frequency of analgesic use and risk of hypertension among men. *Arch Intern Med* 2007; 167: 394–399.
68. Chan AT *et al.* Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation* 2006; 113: 1578–1587.
69. US Food and Drug Administration. Drug Safety Information. 2009; http://www.fda.gov/Drugs/DrugSafety/informationbydrugclass/ucm165107.htm2009. Accessed 12 April 2011.
70. Richmond J *et al.* American Academy of Orthopaedic Surgeons clinical practice guideline on the treatment of osteoarthritis (OA) of the knee. *J Bone Joint Surg Am* 2010; 92: 990–993.
71. Henrotin Y, Chevalier X. Guidelines for the management of knee and hip osteoarthritis: for whom? Why? To do what? *Presse Med* 2010; 39: 1180–1188.