NEW HORIZONS

New horizons in osteoarthritis

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Abstract

Osteoarthritis (OA) is the most common type of arthritis worldwide and rapidly increasing with ageing populations. It is a major source of pain and disability for individuals and economic burden for health economies. Modern imaging, in particular magnetic resonance imaging (MRI), has helped us to understand that OA is a dynamic remodelling process involving all the structures within the joint. Inflammation is common in OA, with a high prevalence of synovitis seen on imaging, and this has been associated with joint pain. MRI detected changes within the subchondral bone are also common and associated with pain and structural progression. Targeting individual pathologies may offer potential new therapeutic options for OA; this is particularly important given the current treatments are often limited by side effects or lack of efficacy. New approaches to understanding the pathology and pain pathways in OA offer hope of novel analgesic options, for example, monoclonal antibodies against nerve growth factor and centrally acting drugs such as duloxetine, tapentadol and bradykinin receptor antagonists have all recently undergone trials in OA. While treatment for OA has until now relied on symptom management, for the first time, recent trials suggest that structure modification may be possible by treating the subchondral bone.

Introduction

Osteoarthritis (OA) is the most common type of arthritis worldwide and is associated with significant morbidity; its prevalence is growing rapidly with ageing Western populations. Joint pain and stiffness, reduced participation in valued activities and poor quality of life, are common for individuals with OA; the burden on health economics has previously been estimated at 0.5–1% of gross domestic product [1]. The last decade has seen major improvements in describing the OA phenotype, through the application of magnetic resonance imaging (MRI), and evidence-based consensus on symptomatic management of OA. This review will highlight some recent developments in our understanding of OA pathogenesis and treatment.

Developments in our understanding of the pathogenesis of OA

Insights at the cellular level

There is increasing data that OA is inflammatory, with a variety of pro-inflammatory mediators being identified in the OA joint, including the interleukins (ILs) and tumour necrosis factor alpha (TNF-alpha). Infiltration of B cells in the synovium and activation of T cells have also been reported [2, 3]. Increased levels of inflammatory cytokines have been noted in both early and late OA, and are produced by the synovium, from activated chondrocytes and osteoblasts [4, 5]. IL-1 and TNF-alpha appear to drive the increased levels of catabolic enzymes, prostaglandins and nitric oxide in the OA joint [6] with recent work suggesting this is due to the activation of synovial macrophages [7]. Inflammation within the OA joint is at least in part the result of a cyclical interaction between damaged cartilage and inflamed synovium. Products of cartilage breakdown are phagocytosed by synovial cells, resulting in an inflamed synovium, which then produces pro-inflammatory mediators. This results in further release of proteolytic enzymes that result in breakdown of cartilage [5].

Insights from genetic studies

OA undoubtedly has a genetic element as has been demonstrated in sibling studies, familial aggregation and twin pair studies; there is a complex interaction between genetic and environmental factors in OA aetiology, with susceptibility differing according to gender and the anatomical site

affected. Susceptibility to OA appears to be influenced by a wide number of genetic variations, for example, in variants of genes which encode for cytokines such as IL-1 and IL-6, and polymorphisms in cytokine and metalloproteinase genes. Polymorphisms in the genes encoding prostaglandins have been associated with OA knee [8, 9] and polymorphisms encoding a specific bone morphogenic protein have been repeatedly associated with an increased risk for the development of knee OA in large and ethnically diverse studies [10–12]. Large genome-wide association studies such as arcOGEN and TREAT-OA have recently identified loci which may confer susceptibility to hip, hand or knee OA. Initial results suggest that OA is a highly polygenic disease with many risk variants [13], but an allele associated with subchondral bone density has been linked with hand OA, supporting a role for the subchondral bone in OA [14].

Insights from modern imaging: pathology is complex

Traditional imaging of OA has relied on the plain radiograph. However, radiographs have limitations, as although symptoms tend to increase as the degree of radiographic structural change increases [15], radiographs can only demonstrate a limited number of structures. While narrowing of the 'joint space' (the measured distance between articulating bones) on radiographs remains the main outcome tool for potential structure modifying drug trials in OA, MR has demonstrated that this space within the knee is dependent not only on hyaline cartilage loss, but also on the degree of both meniscal degeneration and extrusion outside the joint [16].

While radiographs are quick and often more feasible, MRI has the huge advantage of being able to image all the structures within an OA joint, thereby improving our understanding of the association between structural change and clinical symptoms and also assessing the changes within these structures over time. MRI remains largely for use in research studies rather than clinical practice, and specific scoring systems have been developed for quantifying pathological change in multiple tissues across the multiple compartments within a given joint for OA of the hand and knee [17–19]. MRI permits detailed assessment of cartilage, both morphological features and volume, which are useful outcome measures for trials of potential structure modifying drugs [20]. As well, MRI provides a number of techniques for assessing the compositional qualities of cartilage, such as dGEMRIC, which gives a measure of the glycosaminoglycan content of cartilage [21]. Ultrasound (US) has also provided greater insight into OA pathology although it lacks the ability to assess cartilage surfaces as completely as MRI and cannot assess the subchondral bone [22]. US has, for example, demonstrated that osteophytes are much more common in the metacarpophalangeal joints than can be visualised with radiographs [23].

Many large MRI cohort studies have demonstrated that the pathology of OA is far more complicated and involves all the structures within the joint in an active biomechanically driven and biochemically mediated process. The MR imaging pathology of OA is characterised by thinning and focal changes of the articular cartilage, with accompanying subchondral changes of marginal outgrowths of bony ridges (osteophytes), bone marrow abnormalities and cyst formation, and change in the shape of bone referred to as attrition. There is commonly meniscal damage in the knee, ligament tears and weakness of the muscles supporting the joint. Deformity and/or ligamentous damage contribute to mal-alignment of involved joints.

Inflammation is common

Previously thought to be a non-inflammatory arthritis, through the use of MRI and US, we now understand that inflammation is very common within the OA joint. While this may manifest clinically in some patients as a joint effusion, it is now apparent using imaging techniques more sensitive than clinical examination that inflammation of the synovial lining of the joint (synovitis) is almost ubiquitous in knees affected by OA [24, 25] (Figure 1), and is also highly prevalent in hand OA [26, 27]. Histology studies have confirmed that the synovium is abnormal even from the earliest stages of cartilage loss, and that at the time of joint replacement, the synovial lining of an OA joint may be thickened and with inflammatory cell infiltrates and cytokine profiles similar to those seen in rheumatoid arthritis, though often of lesser magnitude [5, 28].

Figure 1. T2 weighted, fat saturated, sagittal image of the left knee demonstrating effusion (in white) in the supra-patellar pouch (long arrow). Synovial thickening is also seen in the tibial-femoral compartment (grey tissue with additional surrounding effusion) (short arrow).

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Imaging studies have noted an association between synovitis and pain within the OA knee and hand joints [24, 26, 29], with recent work demonstrating that pain is increasingly likely as the extent of synovial inflammation seen on imaging increases [24]. Furthermore, joint effusion (a marker of synovitis) has been shown to be an independent predictor of OA progression to total knee joint replacement in a large cohort study [30]. While this may represent an association of synovitis with chondropathy rather than a causative mechanism in progressive cartilage loss, synovitis is clearly worthy of more study.

The subchondral bone is important

Change within the subchondral bone is an integral part of the OA disease process and typical radiographic abnormalities have been described for many years. The subchondral bone in OA has been shown to undergo high turnover with dynamic remodelling using bone scintigraphy [31]. Importantly, MR imaging has identified frequent abnormalities within the subchondral bone termed 'bone marrow lesions' (BMLs), identified as areas of high signal on sequences that suppress the signal from bone marrow fat [32] (see Figure 2). These lesions are not visible on plain radiographs and histology of BMLs has demonstrated these are areas of altered trabecular bone structure and bone marrow fibrosis [33]. Bone is richly innervated and BMLs have been associated with pain in large cohort studies [29, 34] and have also been associated with OA compartment-specific progression of cartilage loss [35].

Although modern imaging has given remarkable insights into the possible peripheral sources of pain in OA, no imaging tool will ever fully be able to fully explain individual joint pain, as OA pain is multifactorial. Not only are there multiple potential structures within a joint that may provide sources of peripheral nociceptive signals, but there may be central pain sensitization in OA [36]. Psychosocial factors are important in how a person perceives pain, and the contextual or placebo response in OA is increasingly common in modern OA trials and of moderate effect size [37]. Furthermore there are limitations in the sensitivity and quantification of pathology detected by current imaging techniques used in OA and a broad variety of patient-reported outcomes are employed in structure-pain association studies.

Current management of OA

Current treatments for OA aim to relieve the pain of OA (symptom modifying drugs), rather than treating the cause of the disease, as no licensed treatments can stop the progression of structural changes within the joint (structure modifying drugs). Current guidelines for the treatment of OA recommend a combination of pharmacological and non-pharmacological treatments [38, 39]. Pharmacological treatments include paracetamol, oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroid injections and non-pharmacological treatments include physiotherapy, splints, acupuncture and the use of a walking aid or brace. While there is good evidence for the effectiveness of some of these treatments, the effect size of most of these treatments for OA is small (see Table 1). For clinical practice, an effect size of 0.2 is considered very small and 0.5 is moderate. Furthermore, compliance with exercise therapies is low and the effectiveness of some treatments, for example, an intra-articular corticosteroid injection, is short lived. NSAIDs and opioids can have significant associated morbidity [40], particularly in the elderly population and given the recent concerns over the safety of paracetamol [41], there is a real lack of safe treatments for those with OA pain.

Figure 2. Proton density fat saturated coronal image of the left knee demonstrating a large high signal (white) bone marrow lesion (arrowed) in the medial tibia.

Table 1. Table demonstrating the effect size for pain relief dependent on the quality of RCT (adapted from Zhang et al. [38])

	All trials ES (95% CI)	High quality trials (Jadad = 5) ES (95% CI)
Acupuncture	0.35 (0.15 to 0.55)	0.22 (0.01 to 0.44)
Paracetamol	0.14 (0.05 to 0.23)	0.10 (−0.03 to 0.23)
NSAIDs	0.29 (0.22 to 0.35)	0.39 (0.24 to 0.55)
Topical NSAIDs	0.44 (0.27 to 0.62)	0.42 (0.19 to 0.65)
Intra-articular HA	0.6 (0.37 to 0.83)	0.22 (−0.11 to 0.54)
Glucosamine	0.58 (0.30 to 0.87)	0.29 (0.003 to 0.57)
Lavage/debridement	0.21 (−0.12 to 0.54)	−0.11 (−0.3 to 0.08)
Chondroitin	0.75 (0.5 to 1.01)	0.005 (−0.11 to 0.12)

New directions for OA therapy

Targeting inflammation

There is mounting evidence for the importance of inflammation within the synovium in OA which support trials of anti-synovitis agents to potentially offer pain relief in OA. An open label study of MTX as an anti-synovial agent for painful knee OA reported that MTX demonstrated good analgesic efficacy for some people with knee OA, although the study was not placebo controlled [42]. A randomised, double blind, placebo controlled study is now underway.

Targeted anti-inflammatory agents, such as monoclonal antibodies against TNF-alpha, have been used in OA trials, and small open label studies of anti-TNF agents have shown some effectiveness in painful OA [43–45]. An open label study of adalimumab for painful knee OA noted at least a 20% reduction in pain in almost two-thirds of the group after 12 weeks of treatment [46]. A recent placebo-controlled study suggested adalimumab may slow progression of structural damage in a subtype of hand OA [47]; however, no change was noted in pain between placebo and treatment arms. This may reflect the patient selection, in that the placebo group had higher baseline pain levels and longer disease duration. However, the preliminary report from a randomised controlled trial of anti-TNF for painful hand OA also noted no clinical improvement at 6 months [48].

Targeting bone

The subchondral bone is a target for OA research as BMLs have been associated with both clinical symptoms and structural progression. While a previous large study did not demonstrate any evidence for the bisphosphonate risedronate in symptom or structure modification (using radiographic outcomes) in knee OA [49], there has been some recent research using bisphosphonates for symptom modification but selecting patients for MRI-detected BMLs. A study of 59 people who received one dose of IV zolendronic acid (ZA) or placebo infusion noted a reduction in the total BML area and a reduction in pain on a visual analogue pain score in the ZA group compared with the placebo group at 6 months [50]. This work suggests that bisphosphonates have potential for symptom and structure modification in OA in a well selected subset.

Other drugs which target the bone have been assessed in OA. A double-blind, placebo controlled phase III study of 1,600 people, using strontium, which can reduce bone resorption as well as increasing bone formation, has recently completed and reported efficacy at both structure modification, with a significant reduction in joint space narrowing and also a significant reduction in the pain score with the highest dose (2 g) of strontium employed in the trial [51]. Calcitonin in knee OA improved function scores in a small 2006 study [52] and a large phase III trial of 1,200 people showed a significant reduction above placebo in all domains of an OA questionnaire [53], although side effects of calcitonin (flushing, gastrointestinal upset) were common.

Targeting nerves

Ongoing research to assess the role of the articular and meniscal cartilage in OA also offers new insights into future treatments. While there is undoubtedly cartilage damage from the earliest stages of OA, it has been unclear as to why this should result in pain, as healthy cartilage is aneural. Interestingly, a recent report suggests that nerve and vascular in-growth occurs in damaged areas of OA cartilage at the osteochondral junction [54, 55]. Increased nerve growth factor (NGF) expression is noted in these vascular channels, which also contain sensory nerve fibres. NGF may increase the sensory nerve activity in the subchondral bone, hence offering a mechanism for both cartilage and subchondral bone as a peripheral source of pain in OA and may offer a target for treatment by a novel class of drugs, the anti-NGFs. The most clinically advanced of this class, tanezumab, is a humanized monoclonal antibody that binds and inhibits NGF and has demonstrated both good analgesic efficacy and improvement in function in a study of 450 people with knee OA [56]. Despite this initial promising data, trials in OA were temporarily suspended due to concerns over accelerated rates of progression to total joint replacement. However, the development of anti-NGF drugs is continuing with rigorous safety criteria included in future trials. Anti-NGF therapies offer potential as the first new class of analgesics in many years.

Targeting central pain

As well as peripheral sources of OA pain that may be targeted for analgesic treatments, there are new treatments for OA that target central pain in OA. Recently trialed therapies include centrally acting drugs such as duloxetine, a serotonin-noradrenaline reuptake inhibitor, for which there is growing evidence. Short-term (10 week) studies of duloxetine versus placebo demonstrated a significant improvement in pain and function for people with painful knee OA already taking NSAIDs [57]. Duloxetine shows promise as a treatment for OA pain and for improving function, but the data specific to OA is currently short-medium term only, however, this drug was recently approved for use in OA by the FDA. Side effects of duloxetine included nausea, dry mouth and constipation, which may limit its use.

Novel opioid drugs are also in development, for example, tapentadol, a centrally acting mu-opioid receptor agonist and noradrenaline reuptake inhibitor. A study of over 1,000 people with chronic low back pain or OA pain, comparing tapentadol with the traditional opioid oxycodone, noted that both drugs provided sustained pain relief but that tapentadol was better tolerated with fewer side effects [58]. Side effects of opioids remain a major disadvantage of this class of drug. The cannabinoid receptors, present in the central and peripheral nervous system and glutamate, a major CNS neurotransmitter, and the bradykinin-2 receptors [59] are also potential targets for pain relief and are under review [60]. Symptom modifying drugs for OA which are undergoing trials or in development are shown in Table 2.

Table 2. Symptom modifying drugs in development for treating osteoarthritis

Drug	Mechanism of action	Target in OA	Reference
Zolendronic acid/bisphosphonates	Inhibition of osteoclasts	Peripheral-subchondral bone	Laslett *et al.* [50]
Strontium ranelate	Dual action bone agent	Peripheral-subchondral bone	Reginster *et al.* [51]
Calcitonin	Inhibitor of osteoclasts	Peripheral-subchondral bone	Karsdal *et al.* [53]
Tanezumab	Monoclonal antibody against nerve growth factor	Nerve growth factor	Lane *et al.* [56]
Duloxetine	Serotonin-noradrenaline reuptake inhibitor	Centrally acting	Frakes *et al.* [57]
Tapentadol	Mu-opioid receptor agonist	Centrally acting	Wild *et al.* [58]
Icatibant	Bradykinin receptor-2 antagonist	Peripherally acting	Song *et al.* [59]
In development…	Targeting the cannabinoid receptors	Centrally acting	Martel-Pelletier *et al.* [60]
In development…	Targeting the glutamate receptor	Centrally acting	Martel-Pelletier *et al.* [60]

Structure modifying therapy in OA

Structural modification in OA remains the 'Holy Grail' in OA research, since, as yet, there are no accepted structure modifying drugs in OA. Results from recent trials mentioned above have suggested structure modification for strontium ranelate and perhaps for calcitonin [51, 53] in OA of the knee. Strontium demonstrated a reduction in joint space narrowing compared with placebo over a 3-year period, as well as an improvement in clinical symptoms [51]. While the study using calcitonin in 1,200 knees did not show a difference in reduction in radiographic joint space narrowing over 2 years, there was an increase in cartilage volume compared with the placebo group [53]. Measuring joint space width by plain radiography is currently recommended by both the FDA and the European Medicine Evaluations Agency as the technique to assessing potential structure modification, but this technique has limitations, not least that the expected average annual joint space narrowing in OA knees is just 0.1–0.15 mm [61]. Hence trials which assess potential structural modifying effects of a drug need to include large patient numbers and be at least 2–3 years long if they are to detect any effect. Using MRI to assess cartilage volume and cartilage thickness, may offer an additional or alternative measure of a drug's structural effects, and studies suggest that MRI can detect significant changes in cartilage morphology over a time period [62] although the best cartilage metrics to use in longitudinal studies still requires further exploration and validation [63].

Summary

Osteoarthritis is the most common type of arthritis worldwide and a major source of pain and disability. Modern imaging has helped us to understand that OA is not simply a degenerate process, but a dynamic remodelling process involving all the structures within the joint.

Current treatments for OA are symptomatic and limited by side effects or lack of efficacy, and despite using the available therapies, many people with OA still have significant symptoms. However, new approaches to targeting pathology offer hope of new analgesic options and for the first time, structure modification may be possible by treating a non-cartilage target, the subchondral bone.

Conflicts of interest

None declared.

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