



## Osteoarthritis

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Osteoarthritis is a major source of pain, disability, and socioeconomic cost worldwide. The epidemiology of the disorder is complex and multifactorial, with genetic, biological, and biomechanical components. Aetiological factors are also joint specific. Joint replacement is an effective treatment for symptomatic end-stage disease, although functional outcomes can be poor and the lifespan of prostheses is limited. Consequently, the focus is shifting to disease prevention and the treatment of early osteoarthritis. This task is challenging since conventional imaging techniques can detect only quite advanced disease and the relation between pain and structural degeneration is not close. Nevertheless, advances in both imaging and biochemical markers offer potential for diagnosis and as outcome measures for new treatments. Joint-preserving interventions under development include lifestyle modification and pharmaceutical and surgical modalities. Some show potential, but at present few have proven ability to arrest or delay disease progression.

### Introduction

Osteoarthritis is the most common joint disease worldwide, affecting an estimated 10% of men and 18% of women over 60 years of age.<sup>1</sup> The pain and loss of function can be debilitating; in developed countries the resultant socioeconomic burden is large, costing between 1.0% and 2.5% of gross domestic product.<sup>2</sup> Traditionally, osteoarthritis treatment consists of pain management with joint replacement for end-stage disease.<sup>3–5</sup> This approach does not address the morbidity associated with early disease or the limitations of arthroplasty surgery, which include the possibility of adverse outcomes and the finite lifespan of prostheses. An improved understanding of the pathogenesis combined with improved assays of disease activity is facilitating a shift in focus to the prevention and treatment of early osteoarthritis. Furthermore, identification of different disease phenotypes might enable personalised care. This Seminar provides an update of developments in the prevention and treatment of early disease.

### Epidemiology

The identification of risk factors is central to understanding the causation of osteoarthritis and selection of targets for prevention and treatment. Longitudinal studies of large population cohorts have provided important insights, and appreciation that osteoarthritis develops through the action of hostile

biomechanics on a susceptible joint is increasing. Biological pathways within a joint are mechanosensitive,<sup>6</sup> and biomechanical factors could be modifiable and offer a potential means of intervention.

Joint biomechanics are dictated by anatomical and functional factors. Anatomical factors include joint morphology. Hip dysplasia, when acetabular coverage of the femoral head is reduced, is a long-established risk factor for osteoarthritis.<sup>7</sup> Femoroacetabular impingement, in which contact between the proximal femur and acetabulum is abnormal, can confer up to a ten-fold increased risk that end-stage hip osteoarthritis will develop within 5 years (figures 1 and 2). The positive predictive value ranges from 6% to 25%, depending on the characteristics of the cohort and the definition of abnormal morphology, whereas the negative predictive value is 98–99%.<sup>8</sup> Similarly, tibial and femoral bone morphology can predict the development of knee osteoarthritis.<sup>9</sup> Limb alignment also seems to be crucial; evidence is accruing that varus and valgus knee alignment increases the risk of development and progression of osteoarthritis in the more loaded region of the joint.<sup>10,11</sup> Furthermore, with leg length inequality of 1 cm or greater the risk of knee osteoarthritis is almost two times higher in the shorter than in the longer limb.<sup>12</sup> With respect to functional factors, poor quadriceps function can increase the risk of progression of knee osteoarthritis.<sup>13</sup> Sporting activity is a recognised but poorly defined risk factor for hip osteoarthritis,<sup>14</sup> and high intensity of activity during adolescence might promote the development of femoroacetabular impingement morphology.<sup>15</sup>

Despite these strong associations, most individuals with abnormal joint biomechanics do not develop osteoarthritis.<sup>8</sup> Susceptibility is partly determined by systemic factors. Age is the strongest risk factor for osteoarthritis;<sup>16</sup> it could indicate a reduction in regenerative capacity and accumulation of risk factors. Osteoarthritis is more common in women than in men; although the role of oestrogens has been widely investigated, the mechanism remains unclear. The material properties of bone could confer some

#### Search strategy and selection criteria

We searched PubMed with the search term “osteoarthritis” in combination with the terms “cartilage”, “bone”, “synovium”, “epidemiology”, “genetic”, “imaging”, “biomarker”, and “treatment”. We focused on publications from the past 3 years (between December, 2010, and December, 2013) but did not exclude important older publications. Emphasis was placed on articles addressing osteoarthritis of the knee, hip, or hand. Published abstracts were not considered. Review articles are cited to provide readers with a detailed discussion of topics outside the scope of this Seminar.

susceptibility. High systemic bone mineral density seems to increase the risk of incident osteoarthritis but not disease progression.<sup>17</sup>

Injury can cause bone or cartilage damage that makes the joint more susceptible to further insult, and damage to ligaments or meniscus can adversely affect joint biomechanics. Knee injury increases the risk of knee osteoarthritis by more than four times.<sup>18</sup> Obesity increases the load on weight-bearing joints, but might also increase joint susceptibility through the action of inflammatory adipokines.<sup>19</sup> It increases the risk of knee osteoarthritis by more than three times<sup>20</sup> and accelerates disease progression.<sup>21</sup> Why the risk of osteoarthritis associated with obesity is much smaller for the hips than for the knees remains a mystery.<sup>22</sup> The increasing prevalence of obesity means that the disease burden is substantial.

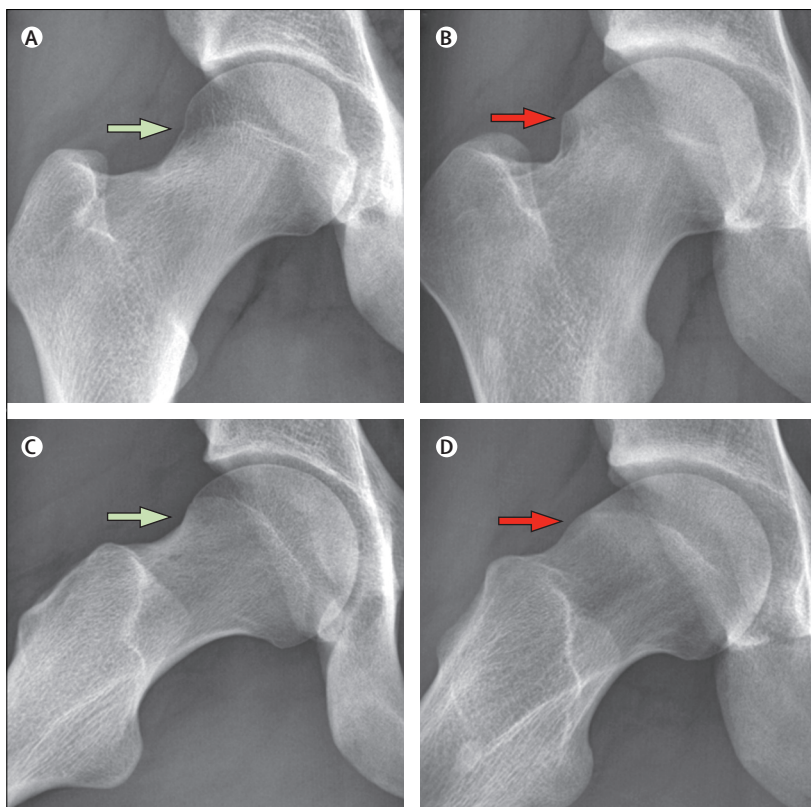
The strong genetic basis for osteoarthritis has been known for many years through family-based studies. Genome-wide association studies, such as that by the Arthritis Research UK Osteoarthritis Genetics (arcOGEN) Consortium,<sup>23</sup> have now identified 11 loci associated with osteoarthritis. The effect sizes are small (odds ratios 1.11–1.21), but consistent with those for other similar complex traits. Genomics alone is unlikely to be able to reliably identify individuals who will develop disease, but it might reveal new biological insights into disease pathogenesis for individual joints. Single-nucleotide polymorphisms have been associated with several known risk factors, including hip shape, body-mass index, and bone mineral density.<sup>24</sup>

### Pathogenesis

Osteoarthritis was once viewed as a disease of purely mechanical cartilage degradation, but it is now known to be a complex condition affecting the whole joint, in which activation of matrix proteases has a pivotal role (figure 3). The possibility that diverse risk factors give rise to osteoarthritis through a common end pathway offers therapeutic potential. Cartilage, subchondral bone, and synovium probably all have key roles in disease pathogenesis, and an association with systemic inflammation could also be present.

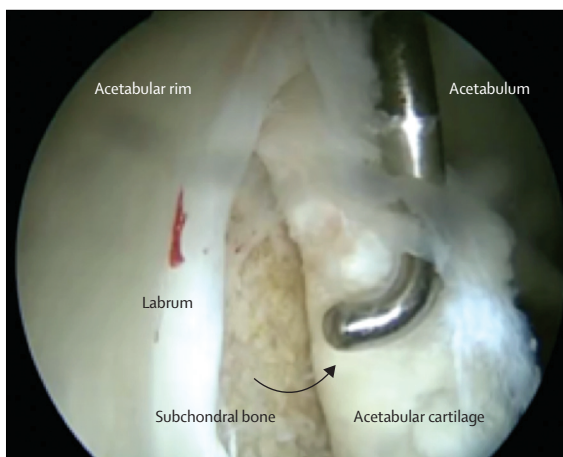
### Cartilage

The main structural protein of cartilage is type II collagen, which provides a meshwork that receives stabilisation from other collagen types and non-collagenous proteins, such as cartilage oligomeric matrix protein, and provides cartilage with tensile strength. Aggrecan and other proteoglycans are embedded within this framework, and draw water into the cartilage, providing compressive resistance. Cartilage architecture and biochemical composition are strictly regulated by chondrocytes in response to changes in their chemical and mechanical environment.<sup>25</sup> On activation, they produce several inflammatory response proteins, such as cytokines, including interleukin 1 $\beta$ , interleukin 6, and tumour



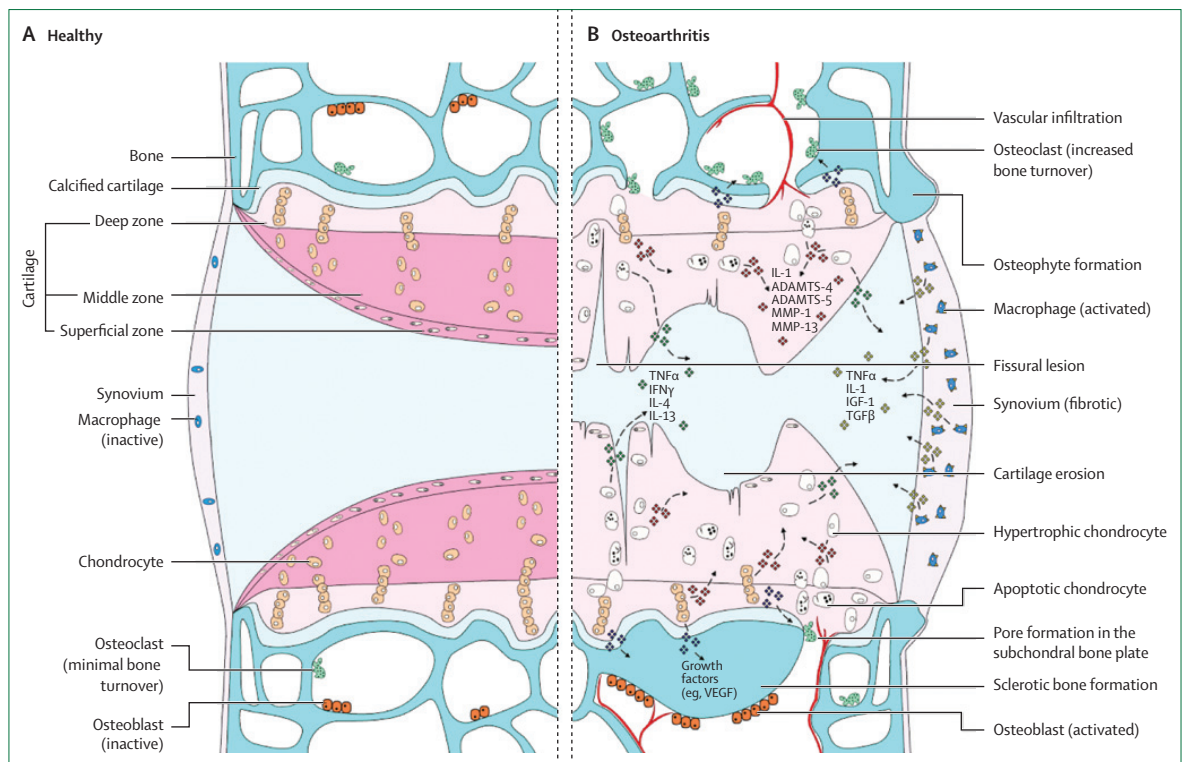
**Figure 1: Anteroposterior and lateral radiographs of a normal hip (A and C) and a hip with cam lesion femoroacetabular impingement morphology (B and D)**

In a normal hip, the concavity of the femoral head-neck junction (green arrow) allows an extensive range of hip movement without impingement of the femur against the acetabular rim. In cam lesion femoroacetabular impingement, the loss of this concavity at the anterosuperior head-neck junction (red arrow) results in impaction of the femur against the acetabular rim when the hip moves into flexion and internal rotation. Resultant damage to the labrum can progress to involve the acetabular cartilage, with development of osteoarthritis. Surgery to excise bone and reproduce a head-neck concavity is proposed as a means of preventing the development and progression of hip osteoarthritis.



**Figure 2: Arthroscopic appearance of the hip of a patient with cam lesion femoroacetabular impingement**

The aspherical femoral head enters the acetabulum on hip flexion and internal rotation, leading to delamination of the acetabular cartilage from the underlying subchondral bone and the development of osteoarthritis.



**Figure 3: Signalling pathways and structural changes in the development of osteoarthritis**

ADAMTS=a disintegrin and metalloproteinase with thrombospondin-like motifs. IL=interleukin. MMP=matrix metalloproteinase. TNF=tumour necrosis factor. IFN=interferon. IGF=insulin-like growth factor. TGF=transforming growth factor. VEGF=vascular endothelial growth factor.

necrosis factor (TNF)  $\alpha$ , and matrix-degrading enzymes including the metalloproteinases and a disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS). Some of these compounds, such as the collagenases (metalloproteinases 1, 3, and 13) and aggrecan-degrading enzymes (ADAMTS 4 and 5), seem to have important pathogenetic effects. Others seem to have beneficial matrix remodelling roles in healthy cartilage.<sup>6</sup> Proteases, including ADAMTS 5, are upregulated in a highly mechanosensitive way in mice after surgical joint destabilisation, and are downregulated on joint immobilisation.<sup>26</sup> These findings suggest the potential to address hostile joint biomechanics as a preventive strategy.

The innate immune system is activated in osteoarthritis. Chondrocytes express many toll-like receptors,<sup>27</sup> which are activated by damage-associated molecular patterns. In osteoarthritis, these patterns consist of extracellular matrix molecules that include the glycosaminoglycan hyaluronan.<sup>28</sup> Calcium pyrophosphate and sodium urate crystals also bind chondrocyte toll-like receptors and might therefore play a part in the aetiology of osteoarthritis.<sup>29</sup> The finding that the expression and activation of complement are abnormally high in human osteoarthritic joints<sup>30</sup> is intriguing. Cartilage oligomeric matrix protein is a potent activator of the alternative complement pathway,<sup>31</sup> whereas proteoglycans such as fibromodulin target the classic pathway.<sup>32</sup> Chondrocytes also express receptors that bind

advanced glycation end products,<sup>33</sup> which accumulate in ageing tissues. This process results in a phenotypic shift to catabolism<sup>34</sup> and could help to explain the increasing prevalence of osteoarthritis with age.

These responses to extracellular matrix components might simply reflect amplification of established cartilage degradation. Chondrocytes could first be activated by inflammatory signals originating from other joint structures such as synovium or subchondral bone. Elucidation is warranted since therapeutic interventions are more likely to be effective when acting early rather than late in the process.

### Subchondral bone

Subchondral cortical bone forms an interface between the calcified cartilage below the tidemark and the underlying trabecular bone. Pronounced changes from normal are seen in the structure and composition of both the cortical plate and trabecular bone in osteoarthritis.<sup>35,36</sup> Features of endochondral ossification are reinitiated in osteoarthritis and the tidemark advances, with associated vascular penetration. This process is accompanied by the formation of osteophytes and subchondral cysts. Advances in imaging now allow bone-marrow lesions to be identified on MRI that are related to several histological changes, including microfractures at different stages of healing.<sup>37</sup> These lesions localise to areas with the most

severe cartilage damage. Some studies suggest that changes in subchondral bone and osteophyte formation precede cartilage degeneration,<sup>38,39</sup> but such studies are biased by the sensitivity of the detection method.<sup>40</sup> A 2012 study showed that osteoblasts respond to mechanical stimulation with the expression of inflammatory cytokines and degradative enzymes, as chondrocytes do.<sup>41</sup> These factors could act directly on cartilage, or changes in the mechanical properties of subchondral bone might have adverse effects on overlying cartilage. Conversely, subchondral bone remodelling might result from increased loading through loss of cartilage integrity. Subchondral bone is highly innervated and probably contributes to the generation of pain in disease.

### Synovium

Synovitis is a common feature of osteoarthritis, even in early disease. In established osteoarthritis, proliferation of synoviocytes and tissue hypertrophy are notable, with increased vascularity.<sup>42</sup> Synoviocytes synthesise lubricants such as hyaluronic acid<sup>43</sup> and lubricin.<sup>44</sup> These contribute to optimum joint function but show reduced lubricating capacity in subsets of patients with osteoarthritis.<sup>43,45</sup> Synoviocytes, like chondrocytes and osteoblasts, also release inflammatory mediators and degradative enzymes. Activation is probably secondary to inflammatory mediators and cartilage matrix molecules released during an initial insult to the joint, after which synovial tissue drives progressive joint degeneration in a positive feedback cycle.<sup>42</sup> Synovitis predicts the development and progression of symptoms (odds ratio [OR] 9·2, 95% CI 3·2–26·3)<sup>46</sup> and possibly cartilage loss (2·7, 1·4–5·1),<sup>47</sup> although the relation with structural change is less consistent. Comparison of study findings is difficult because populations of patients and methods of diagnosing synovitis vary. However, synovitis is a rational target for intervention.

### Systemic inflammation

Osteoarthritis is mainly seen as a local disease confined to the joint, and studies investigating the relation with systemic markers of inflammation yield conflicting results. A 2013 systematic review suggested that serum C-reactive protein is associated with symptoms rather than with radiographic osteoarthritis,<sup>48</sup> and pain could be a marker of systemic inflammation.<sup>49</sup> Why obesity is a risk factor for osteoarthritis in non-weight-bearing joints is not understood.<sup>30</sup> Adipokines released from adipose tissue have been proposed as mediators of this effect, but their role is speculative and not supported by clinical studies.<sup>51</sup>

### Diagnosis

The clinical diagnosis of osteoarthritis can be made only if the patient has symptoms, and the prevention or alleviation of these is the goal of any intervention. Indeed, symptoms are the prompt that leads patients to seek medical attention outside screening or research programmes. The difficulty of using symptoms to define

the presence of osteoarthritis is that they can develop only once the disease is advanced and probably irreversible. This stage might follow a period of subclinical structural change. For disease modification, symptoms therefore have limited value in diagnosis of early osteoarthritis, when intervention is more likely to be successful. Further limitations are that symptoms fluctuate substantially over time and are influenced by concurrent pathology and pain pathway modulation.<sup>52</sup>

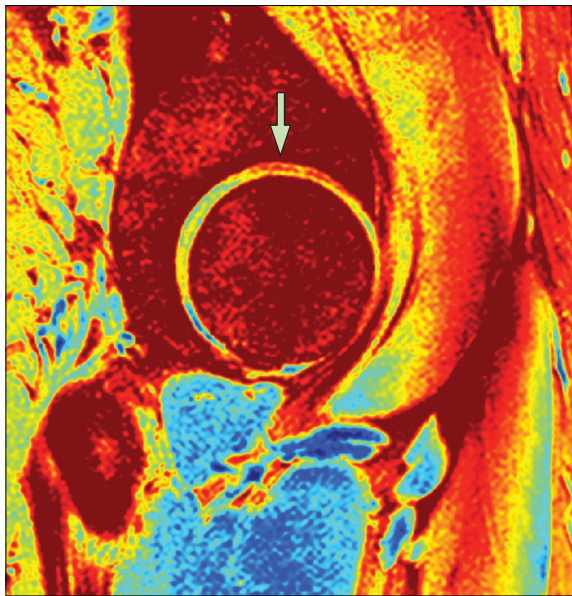
Here, we define structural osteoarthritis as evident cartilage loss without inflammatory or crystal arthropathy, irrespective of whether the patient has symptoms. This definition aims to describe osteoarthritis at an early stage. Although cartilage changes might be preceded by changes within synovium and bone, cartilage degeneration seems to be the common endpoint of all osteoarthritis phenotypes. As understanding of disease pathogenesis improves, measures relating to other joint structures are likely to gain validity. The greatest limitation of addressing structural osteoarthritis is our inability to predict whether it will progress to clinical osteoarthritis.

Interventions used when patients have few or no symptoms must have a low-risk profile and proven effectiveness to be ethically acceptable. With the poor relation between symptoms and structure,<sup>53</sup> clinical benefit from treatment of structural osteoarthritis is not guaranteed. Therefore, studies trying to target the earliest osteoarthritis by modifying structural disease must also take symptoms into account.<sup>54</sup> Symptoms are measured quantitatively with validated patient-reported outcome measures. Structural osteoarthritis is assayed by a rapidly expanding array of biomarkers (appendix). This expansion has been driven by advancing technology, an appreciation that osteoarthritis is a condition of the whole joint, and a need to diagnose the earliest disease to facilitate selection of patients into clinical trials and to measure treatment effectiveness.

### Imaging

Osteoarthritis is traditionally diagnosed with plain film radiography; features include narrowing of the joint space width, osteophyte formation, and the development of subchondral sclerosis and cysts. Scoring systems include those proposed by Kellgren and Lawrence<sup>55</sup> and the Osteoarthritis Research Society International;<sup>56</sup> however, joint space width alone is more sensitive and reliable than these systems.<sup>57,58</sup> Joint space width is the only structural endpoint accepted by the European Medicines Agency and the US Food and Drug Administration to prove effectiveness of disease-modifying osteoarthritis drugs,<sup>59</sup> yet it has many limitations.<sup>40</sup> It lacks sensitivity and cannot detect localised cartilage damage,<sup>60,61</sup> so it is unsuitable for the detection of early osteoarthritis. The measure also lacks specificity; in addition to cartilage thickness, joint space width in the knee depends on the structural integrity of the meniscus and whether it is extruded from the joint space.<sup>62</sup> Standardisation of image acquisition is essential

See Online for appendix



**Figure 4: Sagittal delayed gadolinium-enhanced MRI of cartilage of the hip of a patient with cam lesion femoroacetabular impingement**

The central circular structure is a sagittal view of the femoral head surrounded by articular cartilage. Although there was no evidence of degenerative change on radiographs or morphological MRI sequences, the arrow points to a linear red region within the acetabular cartilage that indicates glycosaminoglycan depletion and early osteoarthritis at the site of impingement.

because joint space width is strongly influenced by joint positioning.<sup>63</sup> The usually slow progression of osteoarthritis and the limited responsiveness to change means that when joint space width is used as an outcome measure, large cohorts are needed and follow-up should be for at least 2 years,<sup>64</sup> though the duration must be balanced against the risk of participants withdrawing. Despite these limitations, radiography is inexpensive and readily available and continues to have a role in both clinical and research settings.

MRI has many advantages over radiography and allows the assessment of joint structures in three dimensions and at high resolution.<sup>65</sup> As a result, it is more sensitive in detecting early structural changes,<sup>61</sup> and MRI measurements substantially outperform those obtained by radiography.<sup>66</sup> The Osteoarthritis Research Society International now recommends MRI for the assessment of cartilage morphology.<sup>54</sup> Short-term changes in cartilage morphology can reliably predict disease progression in a cohort, but not in an individual.<sup>67</sup> Morphological measurements also cannot take account of functional adaptation<sup>68</sup> or cartilage oedema during the very earliest stages of disease.<sup>69</sup>

Physiological MRI permits detection of the very first changes that occur during osteoarthritis development by assessing the biochemical composition of tissues.<sup>65</sup> Protocols used to assay glycosaminoglycan content include delayed gadolinium-enhanced MRI of cartilage (figure 4), chemical exchange saturation transfer, and sodium scanning. Values obtained by delayed

**Panel: Validated semiquantitative MRI scoring systems for knee, hip, and hand osteoarthritis that assess morphological features of osteoarthritis<sup>81</sup>**

#### Knee

Whole-organ MRI score  
Knee osteoarthritis scoring system  
Boston-Leeds osteoarthritis knee score  
MRI osteoarthritis knee score

#### Hip

Hip osteoarthritis MRI scoring system

#### Hand

Oslo hand osteoarthritis MRI score

gadolinium-enhanced MRI of cartilage correlate well with the histological grade of osteoarthritis<sup>70</sup> and statistically significant changes can be detected within 10 weeks of intervention;<sup>71</sup> physiological MRI is therefore a potential outcome measure. However, the clinical applicability of dGEMRIC is limited by long scanning times and the need for intravenous delivery of nephrotoxic contrast agent.<sup>72</sup> Chemical exchange saturation transfer (CEST) and sodium scanning do not require contrast but are only possible with magnets of ultra-high field strength and dedicated hardware.

Other non-invasive MRI protocols that could be of greater clinical relevance and can be used on conventional MRI scanners are under development. They are mainly responsive to collagen orientation and the behaviour of water content, and include T2 mapping, T2\* mapping, T1Rho, and diffusion techniques. T2 mapping is increasingly used in clinical studies,<sup>73</sup> does not require contrast, and has acceptable scanning times; values are correlated with histological degeneration.<sup>74</sup> It is more sensitive in the detection of early osteoarthritis cartilage lesions than is morphological MRI.<sup>75</sup> Some studies also suggest that baseline values can predict longitudinal structural degeneration (OR 1.58–2.62 for different cartilage regions);<sup>76</sup> however, further validation is needed.<sup>73</sup> T2\* mapping, T1Rho, diffusion-weighted, and diffusion-tensor MRI have been less widely used so far, but potential advantages over T2 mapping<sup>77–79</sup> could lead to greater roles in the future.

The recognition that osteoarthritis is a disease of the whole joint has driven imaging of all joint structures. The predictive value of cartilage measurement for disease progression is increased when non-cartilaginous articular abnormalities, such as bone-marrow lesions, meniscal status, and synovitis, are also taken into account.<sup>80</sup> Scoring systems have been developed for knee, hip, and hand osteoarthritis (panel), which show good reliability and responsiveness in clinical trials.<sup>81</sup>

Ultrasonography shows increasing potential in the investigation of osteoarthritis through its ability to assess synovium, particularly in the hands and knees.<sup>82</sup> CT is

not widely used to diagnose early osteoarthritis, but low-dose and dual-energy CT scanners are broadening the musculoskeletal application of this imaging method.<sup>83</sup>

### Biochemical markers

Both effector molecules, such as cytokines and enzymes, and extracellular matrix constituents, such as precursors or degradation products of collagen and proteoglycan, have potential as biochemical markers. Their concentrations are linked to tissue metabolism and can be measured in blood, urine, or synovial fluid. The BIPED classification<sup>84</sup> stratifies biomarkers as burden of disease, investigative, prognostic, efficacy of intervention, or diagnostic. Many biochemical markers have been proposed, but none are yet sufficiently well validated for use in clinical practice. CTX-II (C-terminal telopeptide of collagen type II) and cartilage oligomeric matrix protein are markers of tissue degradation and are the most widely investigated and best performing biochemical markers across all BIPED categories.<sup>84</sup>

Diagnostic biomarkers aim to identify patients with pathological changes. Concentrations of CTX-II in urine and cartilage oligomeric matrix protein in serum are both higher in patients with osteoarthritis than in healthy controls.<sup>85,86</sup> Sensitivity and specificity are poor for all biochemical markers and worse than those of imaging measures. In knee osteoarthritis diagnosed with the Kellgren-Lawrence score, the reported area under the curve is 0.70 (95% CI 0.57–0.81) for urinary CTX-II, 0.73 (0.58–0.86) for radiographic joint space width, and 0.82 (0.72–0.91) for MRI measurements. Combination of CTX-II with MRI measurements gives an area under the curve of 0.84 (0.77–0.92).<sup>87</sup> When measured systemically, biochemical markers could have originated from any site, hence the predictive value is limited unless disease is confined to the specific joint under investigation, which is rarely the case. Assays of synovial fluid overcome this difficulty, but are limited by acceptability to patients and the potential absence of an effusion. Post-translational protein modification might be joint-specific and further investigation is warranted.<sup>88</sup>

The potential value of prognostic biochemical markers is large and could allow the identification of patients most likely to benefit from intervention. Urinary CTX-II and serum cartilage oligomeric matrix protein concentrations have predicted the incidence and progression of radiographic hip and knee osteoarthritis reasonably well in longitudinal cohort studies.<sup>89–91</sup> The predictive value of urinary CTX-II (OR 3.2) is greater than that of joint space width (OR 1.4), but lower than that for MRI measurements (OR 4.8). The combination of CTX-II with MRI measurements has the greatest prognostic value for progression of structural knee osteoarthritis (OR 5.8).<sup>87</sup> Biochemical markers have little ability to predict symptoms.<sup>91</sup> The interpretation of assay results is

	Outcome	Comments
<b>Lifestyle modification</b>		
Weight loss; <sup>95–98</sup> exercise <sup>99</sup> (strength and aerobic capacity)	Symptom improvement and reduced risk of symptomatic osteoarthritis	Potential role as primary prevention strategy
<b>Surgical modification of joint biomechanics</b>		
Periarticular osteotomy <sup>100,101</sup> (to correct mechanical axis of knee or orientation of acetabulum)	Established technique for improvement of symptoms and probably joint survival	Suggested potential for cartilage regeneration after these procedures
Debridement of FAI lesions <sup>102</sup>	Symptom improvement sustained beyond 5 years	Small cohort studies only; structural modification not yet shown; RCTs underway
Joint distraction <sup>103</sup> (6–12 weeks)	Sustained symptomatic improvement with evidence of cartilage regeneration	Best evidence so far that cartilage can regenerate in an osteoarthritic joint
<b>Regenerative surgical techniques</b>		
Microfracture of subchondral bone <sup>104</sup>	Slight improvement in pain and defect filling	Produces mechanically inferior fibrocartilage rather than hyaline cartilage
Cell-based therapies <sup>104,105</sup> (autologous chondrocyte implantation)	Slight improvement in pain and defect filling	Might provide more durable repair tissue than microfracture but further studies are needed; technique is expensive
<b>Pharmaceutical: targeting cartilage degradation</b>		
Glucosamine and chondroitin; <sup>106</sup> hyaluronic acid <sup>107</sup>	Meta-analyses do not show improvement in symptoms or structure over placebo	Conflicting results from different studies
Doxycycline <sup>108</sup>	Structural modification but no symptomatic benefit	Limited by side-effects
FGF-18 (intra-articular) <sup>109</sup>	Structural modification but no symptomatic benefit	Primary outcome measure of structural change in medial compartment not shown
<b>Pharmaceutical: targeting bone remodelling</b>		
Strontium ranelate <sup>110</sup>	Improvement in symptoms and structure	Limited by side-effects

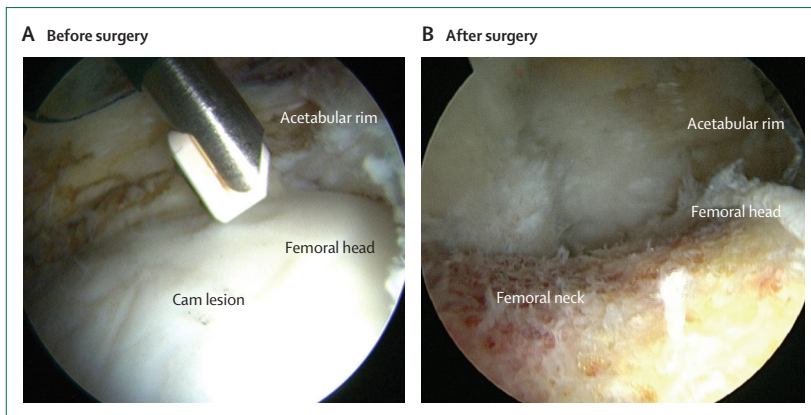
FAI=femoroacetabular impingement. RCT=randomised controlled trial. FGF=fibroblast growth factor.

**Table 1: Summary of treatment strategies that have shown potential disease-modifying properties**

constrained by incomplete understanding of the biological activity they signify and whether it is relevant to clinical osteoarthritis.<sup>92</sup> Further validation is essential since biochemical markers are already widely used as outcome measures in clinical studies to assess effectiveness of intervention.<sup>93</sup>

The number of investigative biomarkers has increased rapidly with expansion of proteomics. Interestingly, a proteomic study of cartilage identified biomarkers that seem to be joint-specific.<sup>94</sup>

The future of biochemical markers is likely to consist of broad-spectrum panels of assays that allow the assessment of osteoarthritis with disease phenotyping to identify the appropriate therapy. The value might be greater if the markers are combined with imaging and genotyping. At present, clinical application is a fairly distant prospect and many obstacles remain. Sampling technique is crucial, and concentrations of biochemical marker are determined by factors including diet, physical activity, and systemic metabolism.



**Figure 5: Arthroscopic appearance of the femoral head-neck junction in a patient with cam lesion femoroacetabular impingement before and after surgical correction of the deformity**

The preoperative image shows the cam lesion (red arrow on figure 1) adjacent to the acetabular rim, above which a radiofrequency ablation device is held. The postoperative image shows the head-neck junction after resection of the cam lesion with a burr to recreate the normal concavity of a head-neck junction (white arrow on figure 1). The aim of recreating this concavity is to prevent impaction against the acetabular rim, which is thought to be a major cause of hip osteoarthritis. The hope, therefore is that this procedure might prevent or delay the development of osteoarthritis.

### Treatment

Improved understanding of disease pathogenesis and advances in the investigation of biomarkers have increased the ability to identify patients at greatest risk of disease, diagnose early osteoarthritis, and measure treatment efficacy within a short time. Consequently, many new therapeutic strategies have been proposed and tested in clinical trials (table). None has so far been approved by regulatory bodies, which require concurrent structural modification and symptom improvement.<sup>54</sup>

### Lifestyle modification

Many aetiological factors of osteoarthritis are amenable to lifestyle changes. Weight loss in obese patients reduces the risk that symptomatic osteoarthritis will develop<sup>95</sup> and improves symptoms once evidence of disease is found.<sup>96</sup> Radiographic structural modification has not been shown, although benefits are evident with morphological and physiological MRI<sup>97</sup> and several biochemical markers.<sup>98</sup> The effects of exercise need further elucidation, but activities focusing on improved muscle strength and aerobic capacity improve symptoms (effect size >0.8)<sup>99</sup> and confer benefits in cardiovascular health and all-cause mortality.

### Surgery

Some aetiological factors are amenable to surgery. The progression of osteoarthritis secondary to hip dysplasia is successfully delayed by reorientation of the acetabulum. In addition to sustained symptomatic improvement, hip survival rates exceed 80% at 10 years.<sup>100</sup> Arthroscopic hip surgery to recontour the proximal femur (figure 5) and prevent femoroacetabular impingement has shown symptomatic benefit beyond 5 years and might modify the long-term risk of osteoarthritis;<sup>102</sup> however, evidence so far is confined to small cohort studies.

Knee alignment predicts the development of osteoarthritis in the compartment of greatest loading, hence unloading this compartment offers therapeutic potential. In an interesting study, temporary surgical joint distraction produced symptomatic and structural improvement in end-stage knee osteoarthritis and suggests that reparative potential is retained.<sup>103</sup> Periarticular osteotomies to correct the mechanical axis of the knee show promise, and prospective studies have shown symptomatic improvement extending beyond 10 years.<sup>101</sup> However, in general, evidence for the effectiveness of these interventions is limited. Randomised controlled trials with long-term follow-up are needed to show whether these joint-preserving operations prevent clinical and structural progression of osteoarthritis.<sup>111</sup>

Various surgical strategies aim to repair localised cartilage lesions.<sup>105</sup> Some techniques transplant autologous cartilage and others seek to stimulate regeneration. The terms mosaicplasty and osteochondral grafting describe procedures in which autologous plugs of cartilage and underlying subchondral bone are transplanted from healthy non-load-bearing regions of a joint to areas of damage. These procedures are technically demanding and rely on the availability of healthy cartilage.

Microfracture seeks to stimulate generation of new cartilage at sites of focal full-thickness defects. In this procedure, subchondral bone is traumatised with a pick so that chondroprogenitor cells are released. Although these cells differentiate into mechanically inferior fibrocartilage rather than hyaline cartilage,<sup>105</sup> the technique is inexpensive and easy to do, and is the most widely used regenerative approach.

Since these procedures all have drawbacks, tissue engineering has led to development of more advanced regenerative techniques. Autologous chondrocyte implantation has been in development since the 1980s; chondrocytes are arthroscopically harvested and cultured before implantation into the cartilage defect several weeks later. The technique has undergone several iterations, but whether it confers improved clinical outcomes over more simple techniques such as microfracture remains unclear.<sup>104</sup> The latest developments include use of other sources of cells, including mesenchymal and embryonic stem cells, use of growth factors, and implantation of cells into three-dimensional scaffolds or matrices that support growth, differentiation, and maintenance of a chondrogenic phenotype (appendix).<sup>105</sup> Little evidence exists that the above techniques modify the development of osteoarthritis. Cartilage repair is unlikely to be successful if the joint environment remains biologically or mechanically hostile, but it could provide an important adjunct to the correction of aetiological factors.

### Pharmaceutical drugs

Many patients who develop osteoarthritis do not have identifiable risk factors amenable to intervention. Furthermore, whether the correction of risk factors is

sufficient to reverse a catabolic tissue phenotype is not known. Pharmaceutical agents, especially paracetamol and non-steroidal anti-inflammatory drugs,<sup>112,113</sup> already play a key part in symptom control, but an increasing number of drugs are also under investigation as disease-modifying agents in osteoarthritis.

Chondroitin and glucosamine show anti-inflammatory and anticatabolic properties *in vitro*,<sup>114</sup> and their ability to relieve symptoms or delay structural progression of osteoarthritis has been much investigated in clinical trials. Results have been conflicting, probably because of differences in study designs and populations of patients, investigator bias, or the use of different drug formulations. More positive findings have been reported for glucosamine sulphate than for glucosamine hydrochloride; however, with the assumption that glucosamine is the active ingredient, no explanation exists for this effect.<sup>115</sup> Overall, published work does not indicate that chondroitin or glucosamine have clinically relevant benefits,<sup>106</sup> and they are not recommended in guidelines published by international bodies.<sup>106,113,116</sup> However, both have safety profiles comparable with placebo.

Hyaluronic acid is a glycosaminoglycan found in synovial fluid that acts as a lubricant, but concentrations are lower than normal in osteoarthritis.<sup>45</sup> Hyaluronic acid has been widely used as viscosupplementation administered via intra-articular injections, but debate over efficacy and safety continues. A 2012 meta-analysis concluded that no clinically relevant benefit was proven in terms of pain or function,<sup>107</sup> and no convincing evidence of structural benefit is available. Lubricin, a glycoprotein that acts synergistically with hyaluronic acid,<sup>117</sup> shows lower than normal lubricating capacity in subsets of patients with osteoarthritis.<sup>45</sup> Supplementation restores normal joint lubrication and might be chondroprotective,<sup>45,118</sup> offering therapeutic potential.

Another strategy is to target degradative enzymes. Doxycycline is a potent inhibitor of matrix metalloproteinases; in randomised controlled trials a small benefit was recorded with doxycycline versus placebo in terms of joint space narrowing, but little improvement in pain or function.<sup>108</sup> This small potential benefit seems to be outweighed by adverse events.<sup>108</sup> Other broad inhibitors of matrix metalloproteinases have shown neither structural nor symptomatic benefit, and many result in musculoskeletal toxicity.<sup>119</sup> Upstream intracellular signalling molecules, such as inducible nitric oxide synthase, have also been targeted with disappointing results.<sup>120</sup>

Bisphosphonates have been used in an attempt to reverse the subchondral bone changes seen in osteoarthritis through their inhibition of osteoclast activity. Randomised controlled trials have investigated the effect of risedronate in knee osteoarthritis; urinary CTX-II concentrations were lower with risedronate than with placebo, but no difference in joint space narrowing was detected.<sup>121,122</sup> Furthermore, the symptomatic

improvement seen in one cohort<sup>121</sup> was not reproduced in a larger multinational study.<sup>122</sup> In another study, a single dose of zoledronic acid was shown to improve pain and the size of bone-marrow lesions at 6 months.<sup>123</sup> Strontium ranelate, in addition to osteoclast inhibition and osteoblast stimulation, increases chondrocyte matrix production *in vitro*.<sup>124</sup> A randomised controlled trial showed that strontium ranelate therapy for 3 years reduced radiographic joint space narrowing more than placebo did; the actively treated patients also had modest improvement in symptoms and a reduction in urinary CTX-II concentrations.<sup>110</sup> Further studies of strontium ranelate are needed, but side-effect profiles are likely to limit its clinical usefulness in osteoarthritis.<sup>125</sup>

Several proposed therapeutic agents target inflammation. Intra-articular steroid injections are widely used to improve symptoms, but do not modify structure.<sup>126</sup> Methotrexate is also under investigation in patients with synovitis.<sup>127</sup> The hope that biological agents targeting components of the inflammatory cascade might transform the treatment of osteoarthritis in the same way as that of rheumatoid osteoarthritis<sup>128</sup> has so far been unrealised.

Anakinra, a recombinant antagonist of interleukin-1 receptor, improved symptoms in patients with knee osteoarthritis compared with placebo, but the effect was not sustained beyond 4 days after intra-articular injection.<sup>129</sup> Subcutaneous or intravenous administration of AMG 108, a monoclonal antibody against the interleukin 1 receptor, in patients with knee osteoarthritis gave no clinical benefit; the death of a patient was attributed to neutropenia secondary to this agent.<sup>130</sup> Anti-TNF therapy has also been trialled in osteoarthritis.<sup>131</sup> Adalimumab, a monoclonal antibody to TNF $\alpha$ , has shown no therapeutic effect in hand osteoarthritis,<sup>132</sup> but promising results have been reported in inflammatory knee osteoarthritis.<sup>133</sup> In view of the adverse effects of biological therapies, systemic treatment is perhaps best justified when disease affects several joints, such as in hand osteoarthritis, whereas single-joint osteoarthritis of the knee or hip might be best approached with intra-articular injections of slow-release medication.<sup>134</sup>

Recombinant human bone morphogenetic protein and fibroblast growth factor have been proposed as disease-modifying drugs in osteoarthritis, since they promote cartilage repair *in vitro*.<sup>135</sup> In one clinical trial<sup>109</sup> comparing intra-articular fibroblast growth factor 18 with placebo, no difference was shown in cartilage loss in the medial knee compartment or symptoms, but structural modification was observed in the lateral compartment with growth factor treatment at a year.

Multipotent mesenchymal stem cells are found in healthy and diseased cartilage.<sup>136</sup> Kartogenin promotes chondrocyte differentiation and cartilage repair in animal models of established osteoarthritis.<sup>137</sup> Whether this substance or similar molecules will translate to clinical use remains to be seen.



## Discussion

Improved understanding of osteoarthritis causation and pathogenesis has led to an increasing array of potential targets to prevent disease development and progression. Advances in imaging and biochemical markers facilitate the diagnosis of early disease, and might provide sensitive assays for treatment effectiveness. Nevertheless, effective preventive strategies have not been readily forthcoming.

Of the interventions investigated thus far, lifestyle modifications show the greatest benefit. Maintenance of an optimum weight and regular exercise are cost-effective and also reduce all-cause mortality. Results are awaited from trials investigating the effects of surgical correction of adverse joint biomechanics.<sup>111</sup> Notably, the disease-modifying effect of doxycycline was negated in knees that were varus aligned.<sup>138</sup> Interventions to modify risk factors could on their own prove inadequate if joint tissues have already shifted to a catabolic phenotype. Combination of surgical intervention with pharmaceutical agents might be the optimum strategy.

Key challenges are to define and standardise outcome measures, and to elucidate why the correlation between structure and symptoms is poor.<sup>53</sup> Greater understanding of peripheral and central pain pathways, aided by methods such as functional MRI, could help to solve this puzzle.<sup>52</sup> The limitations of targeting pain alone are highlighted by trials targeting nerve growth factor. Tanezumab and fulranumab are monoclonal antibodies to the growth factor; in randomised controlled trials they were associated with impressive improvements in pain and function compared with placebo.<sup>128</sup> However, a few patients developed rapidly progressive osteoarthritis,<sup>139</sup> which raised the concern that increased joint loading permitted by improved analgesia worsens disease.

Osteoarthritis has several disease phenotypes,<sup>140</sup> and identification and specific targeting of the phenotypes is likely to prove crucial for the successful development of new therapies. Clinical trials investigating the efficacy of an intervention that targets a particular feature of disease pathogenesis, such as synovitis, are less likely to yield positive results in large unselected populations since only a subset of these patients might have disease that is driven by this feature. Accurately defined disease phenotypes enable a personalised approach to treatment. Improvements in the accuracy of predictive models might also allow selection of individuals with minimum symptoms for early intervention. Meanwhile, symptom management in early and moderate disease and arthroplasty surgery for advanced disease remain the mainstays of treatment.

### Contributors

SG-J and AJRP wrote the first draft. All the authors reviewed and edited subsequent drafts. AJRP performed the literature search.

### Declaration of interests

We declare no competing interests.

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