ASPECTS OF CURRENT MANAGEMENT

The assessment of early osteoarthritis

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Treatment strategies for osteoarthritis most commonly involve the removal or replacement of damaged joint tissue. Relatively few treatments attempt to arrest, slow down or reverse the disease process. Such options include peri-articular osteotomy around the hip or knee, and treatment of femoro-acetabular impingement, where early intervention may potentially alter the natural history of the disease. A relatively small proportion of patients with osteoarthritis have a clear predisposing factor that is both suitable for modification and who present early enough for intervention to be deemed worthwhile. This paper reviews recent advances in our understanding of the pathology, imaging and progression of early osteoarthritis.

As the burden of osteoarthritis (OA) rises with increased life expectancy, the need to address diseases of the elderly becomes more pressing. Between 1991 and 2000, the number of primary total hip replacements being undertaken in England increased by 18%, and the number of primary knee replacements more than doubled. Revision hip and knee arthroplasty increased by 154% and 300%, respectively, over this period, and projections to 2010 for primary hip and knee arthroplasty estimate increases of 22% and 63%, respectively. Longer term projections of primary hip and knee arthroplasty in the United States from 2005 to 2030 predict an increased demand of 174% and 673%, respectively. Whereas arthroplasty is usually successful in relieving pain and improving function, it has inherent disadvantages compared with treatment that preserves the joint. Investigation of the cost-effectiveness of early treatment to preserve the natural joint is both worthwhile and necessary. Unfortunately, progress has been hampered by a number of major obstacles that make it difficult to design new treatments and assess their outcome. Our understanding of the early pathology of OA is poor, particularly in terms of reliable assays or biomarkers. Human tissue suitable for study is difficult to obtain. The tissue commonly studied is often obtained as macroscopically less-involved cartilage from patients undergoing arthroplasty. Such tissue may have been altered by previous medical treatment. There are no good animal models that use a single injury to initiate OA is questionable. From a clinical perspective, disease progression is traditionally monitored with radiography, but its correlation with symptoms in early disease is poor. Longitudinal studies that rely on plain radiographs to evaluate treatments are difficult, as measurable progression is slow and not universal. Moreover, they require trial periods of at least two years in large cohorts of patients.

Little treatment is available for early OA. Surgical options to reduce or prevent disease progression may aim to restore normal anatomy, eliminate biomechanical factors, or resurface isolated cartilage defects by grafting. The development of disease-modifying drugs has been disappointing, failing to replicate their success in rheumatoid arthritis and with none meeting food and drug administration (FDA) approval for clinical practice. Clinical trials of drugs in advanced OA aimed at matrix regeneration or preservation have not been successful, at least not using a single agent. This may well be because the mechanical environment remains abnormal and hostile to cartilage regeneration. Sensitive techniques that could detect early OA and reliably monitor its progression would identify patients who may benefit from joint preserving intervention for entry into clinical trials, thereby aiming to reduce the number of patients needing arthroplasty. The identification of those subjects who are likely to progress rapidly would be particularly useful when designing trials. This review outlines recent
advances in imaging technology, biomarker assessment and genetics that may provide outcome measures through which these objectives may be realised.

**Pathology of osteoarthritis**

Although OA is a disease of the whole joint, the primary change is loss of articular cartilage. Bony remodelling, osteophyte formation and synovial, capsular, ligamentous and muscular changes are secondary.

The structure of articular hyaline cartilage and its degeneration in OA has been reviewed by Buckwalter et al. The key to healthy hyaline cartilage is the maintenance of the architecture and composition of the extracellular matrix, under the control of chondrocytes. These highly specialised cells are sparse and isolated, accounting for only 1% of cartilage volume. The matrix consists of a structural framework of macromolecules and tissue fluid. The former are the collagens, proteoglycans and non-collagenous proteins and glycoproteins. The tissue fluid consists of water (80% wet weight of cartilage), small proteins, metabolites and a high concentration of cations that balance the negatively charged proteoglycans.

The collagens form a fibrillar mesh that gives cartilage its morphology and resistance to tension and shear. The predominant collagen is type II (95%) and, together with type XI collagen, forms rope-like fibrils (Fig. 1). Type IX collagen binds to the surface of type II and acts as a bridging molecule between adjacent collagen II fibres. The structure has considerable capacity to reversibly deform under load. Turnover of type II collagen is normally very low, with an estimated half-life of 100 years. Type VI collagen helps the chondrocyte attach to the matrix, and type X collagen is probably involved in mineralisation of cartilage.

There are two major classes of proteoglycan (polysaccharide-protein conjugate) in cartilage, namely large aggregating molecules (aggrecan) and smaller non-aggregating molecules, such as decorin, biglycan and fibromodulin. The aggrecan molecule consists of a central core protein with approximately 100 glycosaminoglycan (GAG, polysaccharide chains consisting of repeating disaccharides
which contain an amino sugar) side-chains of chondroitin sulphate and keratan sulphate, each of which contains 80 to 100 negatively-charged groups. The aggrecan molecules form proteoglycan aggregates by linking with a long central hyaluronan molecule, resulting in a very large complex with several hundred thousand fixed, negatively charged groups. These aggregates fill the voids and are trapped within the three-dimensional collagen framework, creating a high osmotic pressure that maintains fluid within the matrix and impairs its flux, thereby providing compressive stiffness. Also, the negatively charged aggrecan molecules repel each another, resulting in maximal volume expansion. The turnover of aggrecan is closely regulated by the chondrocytes. The non-aggregating proteoglycans (biglycan, decorin, fibromodulin) and other non-collagenous matrix proteins, such as chondroadherin, cartilage oligomeric matrix protein (COMP) and fibronectin, have a variety of roles, including stabilisation of the framework, regulation of fibrillogenesis and matrix metabolism through feedback via interactions with the chondrocyte. Cartilage oligomeric matrix protein is the largest matrix molecule in cartilage after type II collagen and aggrecan. Although it does not bind to collagen II it facilitates fibrillogenesis by cross-linking with neighbouring collagen fibrils. It is more active in early OA, indicating a role in the repair response. Its importance is also highlighted by mutations of its encoding gene that result in pseudoachondroplasia and severe epiphyseal dysplasias.

In healthy articular cartilage the matrix protects the chondrocyte from mechanical damage during normal loading, determines the types and concentrations of molecules that reach the cells and helps maintain their phenotypes. The chondrocyte responds appropriately to changes in the mechanical and biochemical environment by adjusting the degree of synthesis or degradation of macromolecules in order to maintain homeostasis, all under the control of various cytokines. Two groups of enzymes degrade the two major components of the matrix. The matrix metalloproteinases (MMPs), of which MMP-13 is most important, break down type II collagen. Aggrecan may also be degraded by MMPs, but its initial cleavage is by ADAMTS enzymes (a disintegrin and metalloproteinase with thrombospondin-like motifs), specifically ADAMTS-4 and ADAMTS-5.

Cartilage is divided into superficial, middle, deep and calcified zones, which differ in their composition and architecture. The superficial zone has a relatively high collagen and low proteoglycan content, with thin fibres arranged parallel to the articular surface to resist shear forces. This provides a tough ‘skin’ whose integrity is important in protecting the deeper zones. The middle zone has obliquely orientated, thicker collagen fibres with a higher proteoglycan content. The thickest collagen fibres of the deep zone are arranged perpendicular to the articular surface, providing compressive strength and the proteoglycan content is highest in this layer. The calcified layer between cartilage and bone alleviates shear stresses between the two. The line of transition between the calcified and deep zones is termed the tidemark.

The morphology and density of chondrocytes also changes by zone. Their greatest number is in the superficial zone, where they are disc-shaped with long axes parallel to the articular surface. In the middle zone, the cells are more spherical and are isolated or in small clusters distributed randomly in the matrix. In the deep zone they are ellipsoid and form columns of two to six cells that radiate towards the articular surface. In each zone the matrix is divided into three regions according to proximity to the chondrocyte. The pericellular zone is rich in proteoglycans with little fibrillar collagen. The territorial zone contains collagen fibrils that adhere to the pericellular matrix. These two zones serve to protect the chondrocyte mechanically and transmit mechanical signals. Beyond the territorial zone is the metabolically inert interterritorial matrix, which constitutes more than 90% of the cartilage volume and contains the largest collagen fibrils.

**Early pathology**

The first abnormality seen in osteoarthritic cartilage is oedema, which is secondary to disruption of the macromolecular framework and degradation of aggrecan with release of fragments into the synovial fluid, thereby resulting in reduced capacity of the matrix to bind or exclude water. It may be due to mechanical insult, accelerated molecular degradation caused by inflammation or metabolic alteration within the matrix that affects the ability of the chondrocyte to maintain homeostasis. The initial loss of aggrecan allows the remaining proteoglycan molecules to swell, resulting in oedema and softening of the cartilage. The matrix expands, stretching the collagen framework and rendering it susceptible to further mechanical insult, with subsequent breakdown of type II collagen. Softening also facilitates transmission of force to the subchondral bone, increases its stiffness and results in impact load being transmitted to the compromised cartilage. These very early changes are reversible (Table 1), as the chondrocytes can degrade damaged molecules and increase the production of new matrix molecules under the influence of various growth factors. However, during this period the chondrocytes are more vulnerable to apoptosis or necrosis.

The success of the repair response determines the progression of disease. Eventually, if the increased chondrocyte activity fails to repair the matrix, the capacity for repair will decline because of chondrocyte death and a downregulation of response to anabolic cytokines, resulting in an irreversible reduction of the potential to maintain matrix. Inevitably, further depletion and progressive structural damage occurs. Thus, in early disease both anabolism and catabolism are increased, with the balance moving towards catabolism with disease progression. The key event that shifts chondrocyte metabolism towards catabolism and
irreversible disease progression is not well established, although it is suggested that activation of MMP-13 by collagen itself may be important.\textsuperscript{15,16} This is made possible by the depletion of aggregan in the pericellular and territorial matrix environment, which dysfunctions this protective shield around the chondrocyte and allows collagen fibrils to interact with a cell receptor that activates MMP-13. Further evidence for the importance of self-perpetuating catabolic processes which are mediated via MMP-13, has been provided by Yasuda et al,\textsuperscript{17} with a similar role identified for fibronectin fragments by Zack et al\textsuperscript{18} and Stanton, Ung and Fosang.\textsuperscript{19}

The earliest histological changes are fraying or fibrillation of the superficial zone of articular cartilage, reduced staining for proteoglycans, violation of the tidemark by blood vessels and nerves and subchondral bone remodelling. The histopathology, originally described and graded by Mankin et al,\textsuperscript{20} was reviewed by the Osteoarthritis Research Society International (OARSI) group,\textsuperscript{21} who proposed new grades and stages (Tables II and III and Fig. 2), based on histological features of progression. Multiplica-
tion of the grade and stage gives an ‘OA score’ from 0 to 24. The OARSI system has the benefit of a more precise definition of the early changes in OA cartilage (grades 1 to 3) and hence an improved capacity to differentiate between early and mild OA. It is important to emphasise that significant metabolic derangements occur in cartilage prior to superficial fibrillation and that a normal macroscopic appearance does not guarantee absence of pathology.

The traditional assessment of OA relies on features occurring in the late pathological stages. In order to modify progression, earlier detection and new methods of assessment are required.

**Imaging**

Radiography is the recommended imaging modality for assessment of disease progression. Well-established systems grade severity according to joint space narrowing, osteophyte formation, subchondral sclerosis and cyst formation.\(^{23,24}\) For the hip and knee, progression of disease is assessed by measurement of the minimum joint space width.\(^{4,25}\) With respect to early disease these methods are flawed. They rely on an indirect assessment of the status of articular cartilage, which is prone to error.\(^{4,5,26}\) Joint space narrowing will only be apparent when disease has advanced to the erosive stage (OARSI grade 4, Table II and Fig. 2). More sensitive methods are necessary to monitor early disease, and alternative imaging techniques provide the opportunity to examine the morphology of cartilage in detail, assess other relevant structures such as synovium or meniscus, and image the function or biochemistry of cartilage prior to erosive changes.

**Higher sensitivity assessment of cartilage morphology.** CT arthrography is a sensitive method for detecting early structural cartilage lesions\(^{27}\) and may be superior to plain MRI.\(^{28}\) As with MR arthrography, it is inherently invasive, albeit offering the opportunity for intra-articular diagnostic injection of local anaesthetic.

MRI has the advantage over CT in that it can image all tissues within the joint, and its use of specific cartilage sequences\(^{29,30}\) enables a detailed and quantitative assessment of cartilage morphology. Semi-automated separation of cartilage from subchondral bone...
A delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) scan of the knee showing slices from the medial (left) and lateral (right) compartments. The scale (ms) represents the dGEMRIC index ($T_1^{\text{Gd}}$), the colour scale applied to the image facilitates visual interpretation. Higher values of $T_1^{\text{Gd}}$ represent increased glycosaminoglycan (GAG) content. The scan demonstrates the physiological reduction in concentration of GAG as one moves from the deep to superficial cartilage zones, particularly clearly for the tibial cartilage of the lateral compartment. The tibial cartilage of the medial compartment demonstrates a relative depletion of GAGs anteriorly compared with posteriorly, in the absence of chondral erosion, suggesting early anteromedial osteoarthritis (image kindly provided by Dr Deborah Burstein, Beth Israel Deaconess Medical Center, Boston).

and synovial fluid enables the recording of parameters such as cartilage volume, thickness, surface area and roughness, lesion size and depth, and areas of denuded subchondral bone. This assessment appears reliable and appropriate for cross-sectional and longitudinal studies. However, although quantitative MRI is more sensitive than standardised radiography, the detailed information provided estimates the annual loss of cartilage volume in OA of the knee to be approximately 5%, indicating that assessment of disease progression using such techniques will be slow. Furthermore, early intervention will probably need to be in advance of any significant structural cartilage loss. For these reasons there is great interest in the application of MRI to assess changes in the biochemical composition of cartilage before structural damage has occurred.

Imaging of cartilage biochemistry: ‘in-vivo histology’. The biochemistry of the extracellular matrix may be assessed using a number of specific MR techniques. T2 relaxation time mapping demonstrates collagen fibril orientation, quantity and molecular structure. Sodium MRI, $T_1^{\text{rho}}$ ($T_1$ in the rotating frame) and dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) assess the GAG content. Of these techniques, T2 mapping (sensitive to hydration) and $T_1$ may be subject to difficulties with interpretation, and sodium MRI to difficulties with implementation. The dGEMRIC procedure involves the intravenous administration of the ionic contrast agent gadolinium diethylene triamine penta-acetic acid (Gd(DTPA)), which diffuses into articular cartilage through the subchondral bone. The distribution of Gd(DTPA) inversely reflects the concentration of negatively charged GAGs within the cartilage matrix. The $T_1$ relaxation time in the presence of Gd(DTPA), namely $T_1^{\text{Gd}}$, recorded in milliseconds, correlates with the cartilage GAG content, enabling inferences of GAG concentration for specific regions of interest or for the whole joint. The average $T_1^{\text{Gd}}$ for a given region provides the dGEMRIC index (Fig. 3). Concerns about the validity of the dGEMRIC technique relate to variability in the plasma concentration of contrast, its delivery to the joint, which may vary in the diseased state, and the validity of interpretation of the $T_1$ signal. Also, the technique requires a period of exercise following injection and a delay to allow saturation of contrast prior to imaging. A strict protocol must be followed for satisfactory reproducibility in longitudinal studies. Nevertheless, dGEMRIC has the potential to diagnose early OA prior to structural deterioration, and its sensitivity to detect changes in matrix biochemistry is supported by studies examining the response to exercise and changes following anterior cruciate ligament injury. Two studies have applied dGEMRIC clinically in the hip. It was found to predict the likelihood of failure following periacetabular osteotomy for dysplasia and correlated with the symptoms and severity of dysplasia. Likewise, in the knee dGEMRIC may be sensitive to subclinical cartilage disease, and in more advanced disease a reduction in the dGEMRIC index not only correlates with progressive radiological changes but also appears to improve the differentiation of disease within a given radiological grade. Furthermore, the histological capability of dGEMRIC may have advantages over plain MRI for the evaluation of cartilage repair after autologous chondrocyte implantation, potentially negating the need for second-look surgery and biopsy. Thus, dGEMRIC offers great potential as an imaging marker of early OA and, with further evaluation, may find a role in routine clinical practice.
High-frequency ultrasound has recently been introduced as a potential adjunctive tool for cartilage assessment during arthroscopy.\textsuperscript{51-53} Inferences regarding the quality of cartilage may be made by measuring the maximum wavelet magnitude and echo duration.\textsuperscript{51} The echogenicity of cartilage reduces with progressive degeneration in a quantifiable manner, and ultrasound has the added benefit of being able to assess change at the cartilage-bone interface. Ultrasonographic abnormality correlates with histological grade in an animal model.\textsuperscript{53} Ultimately, the sensitivity of this invasive technique in early disease compared with MRI techniques will determine its adoption into clinical practice.

Finally, the importance of subtle variations in mechanical factors, such as joint morphology or alignment, in individuals with no previous history of joint disease is increasingly recognised in the aetiology of OA.\textsuperscript{54-56} It is unlikely to be possible to reverse or arrest disease progression without addressing these mechanical factors.\textsuperscript{5} Therefore, the imaging protocols in trials of novel treatments will need to identify these abnormalities, and decide whether to address them as part of the intervention.

**Biomarkers**

In a clinical trial, progression of disease may be defined according to endpoints that indicate how a patient feels, functions or survives. A surrogate outcome measure may substitute for a clinically meaningful endpoint, wherein lies a role for biomarkers. A biomarker is ‘a structural or physical measure of cellular, molecular or genetic change in a biologic process that can be identified and monitored, with resulting diagnostic or prognostic utility’.\textsuperscript{57} Biomarkers are usually thought of as biochemical substances whose potential applications are in the understanding of disease processes, identification of molecular targets, diagnostic testing, assessment of disease severity and risk of progression, and monitoring the response to treatment.\textsuperscript{57,58} The validation of a biomarker as a surrogate outcome measure would be extremely useful for the evaluation of new treatments and is of particular interest in early disease because of the potential to provide instant information about cartilage metabolism. There are a number of requirements for the validation of a biomarker. Its biology must be understood in terms of its origin, tissue specificity, spatial tissue distribution, metabolism, release from the tissue and clearance. Its assay should measure serum or urine levels, as synovial fluid is less practical, be robust, reproducible, readily available, convenient and cheap. Biomarkers may be classified according to five categories\textsuperscript{59} (Table IV), with further validation against an accepted gold standard test, usually the radiograph, but also clinical outcome in the case of efficacy of intervention markers. Finally, the biomarker must be statistically robust as assessed by its sensitivity, specificity, positive predictive value and likelihood ratios, and relative risks or odds ratios.

There are problems with OA biomarkers. Their validation is difficult and measurement may be confounded by age, gender, ethnicity, body mass index and comorbidity. Their concentration will be influenced by the tissue source and abundance, the amount of synthesis and degradation, the method and efficiency of clearance (which affects measurement from serum or urine more than synovial fluid), inflammation, renal and liver function, diurnal variation and joint movement, food intake (gastrointestinal motility increases circulating levels of serum hyaluronan\textsuperscript{60}) and drug interactions, either by direct interaction with the marker or modifying release at the joint. For these reasons, samples should be taken fasted, early in the morning, and urine samples should be from the second void. The measurement of a biomarker in serum or urine cannot be joint-specific so it assesses the total body burden of degenerative joint disease, not only from synovial joints but also from sources such as the lumbar intervertebral discs.\textsuperscript{61} The interpretation of levels may not be straightforward because in early disease chondrocytes increase their anabolic activity to compensate for degradation, but this increased activity gradually declines with disease progression. Thus, markers of cartilage turnover vary according to stage of disease.\textsuperscript{62} Also, disease progression is phasic rather than linear, which further complicates interpretation of the marker level.\textsuperscript{63} Finally, the gold standard outcome measure of structural radiological change may itself not be valid, given that pre-radiological disease releases biomarkers.\textsuperscript{64} Validation purely against radiographs also ignores clinically important outcomes such as pain and function.\textsuperscript{60}

Many biomarkers have been investigated.\textsuperscript{58,65-67} As OA affects the metabolism of bone, cartilage and synovium, potential candidates include the matrix components, their propeptides which are cleaved off during the conversion to the functioning protein (providing a marker of synthesis), their breakdown products (degradation markers), and cytokines and proteases of these tissues. Synovial, inflammatory and genetic markers should also be considered.

| Table IV. Classification of biomarkers\textsuperscript{59} |
|---------------|-----------------|------------------|
| **Type**       | **Definition**              | **Study design**                     |
| Diagnostic     | Differentiates diseased from non-diseased | Cross-sectional or case-control |
| Burden of disease | Associated with extent or severity of osteoarthritis | Cross-sectional or case-control |
| Prognosis      | Predicts onset or progression | Longitudinal |
| Efficacy of intervention | Indicative or predictive of treatment efficacy | Controlled trial |
| Investigative  | Not yet meeting criteria for another category | Not applicable |
Matrix molecules as biomarkers. Collagen II synthesis may be assessed by measuring the serum level of its propeptides, and there is evidence for reduced levels in OA of the knee. However, as explained above, the interpretation of these markers of synthesis in early disease must be cautious. Also, the different propeptide assays available may show variable specificity according to different body sites. Degradation of type II collagen may be measured in urine by testing for fragments of the helical (Helix-II) or C-telopeptide regions (CTX-II), which are localised primarily to hyaline cartilage. These fragments are released through different enzymatic pathways. Helix-II is a relatively new biomarker and elevated levels are associated with rapidly destructive OA of the hip. CTX-II has been more extensively studied, is raised in osteoarthritic patients compared with controls, is consistently associated with clinical and radiological markers of OA of the hip, and predicts the severity and progression of OA of the knee and hip. Whether it is the optimum marker for early disease is unclear. Although its levels have been shown to correlate with the severity of cartilage defects as assessed by MRI in young patients, an assay for epitope C2C, which is a marker for the initial cleavage of type II collagen, provided better sensitivity to pre-radiological disease but, unlike CTX-II, was unable to differentiate this from radiological disease. This suggests that these markers reflect different mechanisms of degradation and may be involved at varying stages of disease.

CTX-II also shows potential as an efficacy of intervention marker in OA and rheumatoid arthritis, with less progression of disease and symptomatic improvement in OA of the knee treated with risedronate being associated with lower levels of CTX-II. In a larger study, however, the same reductions of CTX-II with risedronate were not associated with an improvement in symptoms or slowing of radiological progression. The suggested mechanism of action of risedronate in OA is through the inhibition of subchondral bone turnover, which directly or indirectly results in a reduction of articular matrix degradation or calcified cartilage turnover.

Markers of aggrecan turnover have great relevance for early OA. Assays for synthesis and degradation markers have been developed, but have mostly been assessed in ex vivo cartilage explants or synovial fluid. There is a lack of clinical data from the serum or urine of OA patients available for validation.

Cartilage oligomeric matrix protein has been extensively studied as a possible biomarker. Elevated serum levels of COMP occur in OA of the knee and are associated with reduced cartilage volume and disease progression. However, COMP is not exclusive to cartilage and is also present in other connective tissues, such as the synovium and meniscus. Increased serum COMP reflects synovitis in the hip and knee, indicating a lack of specificity which necessitates cautious interpretation of its role as a biomarker.

Synovial and inflammatory markers. Hyaluronan is a major product of synovial cells, providing the viscosity of synovial fluid. When measured in serum, it is considered a marker of synovitis. Despite its widespread expression in connective tissue, hyaluronan appears useful as a biomarker for both OA and rheumatoid arthritis. It is associated with progression of OA in the knee and hip, particularly when combined with CTX-II.

C-reactive protein (CRP) is a non-specific marker of inflammation but is elevated in OA using highly sensitive assays and is associated with disease progression. Most studies include its measurement in their protocols.

Current recommendations. The maintenance of the musculoskeletal system depends on the balance of synthesis and degradation. From the biomarker perspective, this was exemplified by the study of Garnero et al on type II collagen, where the progression of OA of the knee was eight times faster in those individuals that demonstrated simultaneously decreased synthesis and increased degradation. Although most studies have examined subjects with established OA, there is evidence from the canine cruciate transection model that measuring biomarkers from serum and urine is sufficiently sensitive and specific to be of use in early disease. Because of the overlap in the level of single markers between healthy controls and subjects with OA, longitudinal monitoring of a combination of biomarkers to simultaneously account for synthesis and degradation is superior for assessing the progression of disease.

Genetic markers. There has been significant progress in the field of genetic susceptibility to OA in recent years, through two investigative strategies, namely genome-wide linkage analysis in families with a history of OA and candidate gene association studies in unrelated individuals. Genes predisposing to OA have been identified, the majority of which encode for regulatory rather than structural proteins. The increased risk of OA of the hip and knee in siblings of patients with the disease is well established, and this risk is also passed on to their offspring. A few studies have highlighted a familial link not only in the development of OA but, perhaps more importantly, in disease progression. Having identified a gene, its function and interactions may then be explored, leading to improved understanding of the pathology of OA at the molecular level and the identification of potential therapeutic targets. Also, the validation of genetic markers as prognostic biomarkers provides the opportunity to genetically screen an individual and determine their probability of developing progressive disease. Such genetic markers have been achieved for rheumatoid arthritis but are not yet specified for OA.

In conclusion, there is a need for earlier intervention in OA to prevent progression to joint replacement. Current assessment is based on histologically advanced disease, and the investigation of novel treatments is likely to be impossible with traditional methods. The new assays of early disease described in this review offer promise. They require...
validation in longitudinal studies of carefully selected patient cohorts. The importance of mechanical and biochemical factors to the aetiology of OA emphasises the key role orthopaedic surgeons will have in identifying the patients, developing the treatments, and realising the benefits over the next century.

References


