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Osteoarthritis: pathogenesis and prospects for treatment

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Editorial

Our understanding of osteoarthritis has moved forward considerably over recent years. In recognition of this Hands On and Topical Reviews have joined together to give a comprehensive overview of this important and common problem.

Hands On* focuses on the sea change in the way that we think about osteoarthritis. We have moved on from the concept of joint degeneration and affected patients need a holistic approach. As well as an update about core treatments the authors give very practical advice on how to approach explanation and provision of information. Patients tell us that what they want is greater support with self-management.

Topical Reviews gives a detailed account of current surgical approaches and delves into the basic biology of osteoarthritis as a process of 'tear, flare and repair'. The authors examine how a better understanding of cell biology and biomechanics may lead to better medical and surgical treatments.

Together, these publications shift the emphasis from passive, symptomatic treatment to active, patient-focused management underpinned by sound evidence.

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Simon Somerville (Medical Editor, Hands On)

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* Porcheret M, Healey E, Dziedzic K, Corp N, Howells N, Birrell F. Osteoarthritis: a modern approach to diagnosis and management. Reports on the Rheumatic Diseases (Series 6), Hands On 10. Arthritis Research UK; 2011 Autumn. www.arthritisresearchuk.org/medical-professional-info.

Introduction

Osteoarthritis (OA) is the commonest form of joint problem, with symptoms affecting over half of the population over 60 years.[1] The prevalence of radiographic changes at ≥63–65 years is high: around 70% for hand OA, 33% for knee OA and 10% for hip OA, with around half getting significant symptoms or disability (prevalence of symptomatic hand OA 30%, knee OA 15% and hip OA 5%) and a lifetime risk of OA-specific morbidity of about 45% for the knee and 25% for the hip.[2] This leads to 164,000 hip and knee replacements in England and Wales per year[3] and costs the NHS at least £1 billion per annum, although estimates including the indirect costs (including lost work and benefits) suggest the total cost to the UK economy is around 1% of gross national product (GNP).[4] One important recent finding has been the report in a prospective cohort study of a significant 55% excess mortality from OA.[5] This problem is therefore a high priority for health professionals – including general practitioners and practice nurses (500 patients on a typical 10,000 practice list consult every year),[6] physiotherapists (who deliver key exercise interventions), occupational therapists (who assist with activity restrictions), dietitians, orthopaedic surgeons (who perform joint replacement surgery), rheumatologists (who may be more involved in education and service development rather than seeing lots of OA patients) and other physicians and surgeons (where it is a common co-morbidity for those presenting with other acute or chronic illnesses).

The aim of this report is to provide a comprehensive overview of OA. It will cover our current understanding of the pathophysiology, how this translates into potential future treatments and a review of current surgical practice and its evidence base.

Defining OA

There are various definitions for OA, of which the most useful clinically is that used for the associated Hands On report[6] – essentially the majority of peripheral joint pain in older adults (especially at the knee, hip, hand and foot), once the rarer types of arthritis where inflammation is predominant (e.g. rheumatoid arthritis and psoriatic arthritis) are excluded. While Hands On focuses on the biopsychosocial perspective that we recommend in a clinical setting, few scientific studies have included this perspective. For population studies, different definitions are used including the presence of typical radiographic change alone,[1] although the presence of pain plus radiographic change is more useful.[7] Classification criteria exist for knee, hip and hand OA,[1] but are most applicable to enrolment of subjects in clinical trials and the generalisation of data from such studies. Equally, emerging magnetic resonance imaging (MRI) definitions[8] are not of practical use to clinicians, as MRI is not clinically justified. Based on a growing consensus on the pathogenesis of OA, discussed below, we propose that OA be concisely described as a disease of 'tear, flare and repair'. This encompasses the key aetiologic role of trauma and mechanical imbalance; the role of inflammation in pain and progression; and the role of repair processes in and around the joint.

Pathogenesis

There is a substantial evidence-base for the factors involved in the initiation and some evidence for progression of OA.[9] Important caveats are that these risk factors vary by site and, as with other conditions, there is difficulty in extrapolating animal model data (such as cruciate ligament transection or the transgenic murine OA model constitutively expressing human matrix metalloproteinase-13 (MMP-13)) to humans, although these studies have suggested potential targets for therapy such as MMPs (especially MMP-3 and MMP-13) and a disintegrin and metalloproteinase with thrombospondin motifs (e.g. ADAMTS5).[10] Figure 1 summarises the main pathogenetic pathway. While the phrase 'wear and tear' is often used to describe the aetiology, this is inaccurate. If wear were a major factor, the lifetime prevalence would be expected to tend towards 100% at a particular age for each site affected. Instead, the epidemiological data show discrete risk groups who develop early severe disease related to load and use in a pattern consistent with microtrauma or frank injury. For example, at the knee key factors for initiation are meniscal injury or malalignment. There is now prospective data showing that meniscal or inflammatory changes demonstrated on MRI are predictive of the subsequent development of OA.[11] In the older population ageing changes in the musculoskeletal system contribute to the development of OA by making the joint more susceptible to the effects of other OA risk factors with the effects mediated by inflammation.[12] The data for each of these key pathogenetic steps is reviewed below under the following headings: biomechanical factors, inflammation in/around joint, biochemical mediators, and bone response. A large body of evidence, including familial aggregation and classic twin studies, indicates

that primary OA has a strong hereditary component that is likely to be polygenic in nature. Many candidate genes have been identified, differing by site of OA, and several studies have been replicated, but the effects are small and the proportion of those with OA who have these variants is low. There have been attempts to realise the potential clinical relevance of genetic susceptibility to OA,[13] through associations with factors such as the transforming growth factor β (TGFβ) pathway (e.g. GDF5, asporin and SMAD3), and genome-wide association studies have reported several low-association signals, which include some TGFβ pathway components; their relevance to prognosis and treatment remains limited at present.[14]

Biomechanical factors

The most potent factors driving the development of OA are biomechanical: congenital dysplasia of the hip;[15] complete or partial rupture of cruciate or collateral knee ligaments[16] – although associated meniscal injury may be the critical risk factor;[17] or fracture through the articular surface,[18] for example. These models of early and severe disease are vulnerable to the criticism that they are different diseases from primary or idiopathic OA, but some of the evidence is now suggesting that common biomechanical factors, such as mild developmental abnormalities, are key to the development of primary OA.[12] Certain occupational associations are also instructive, in defining joint-specific disease associated with high loads – the hip in farmers, the knee in professional footballers, and the hand in millworkers.[1] The epidemiological evidence for sport extends this further to allow the likely risk of leisure activities to be estimated – for example, the consistent association of heavy physical activity and running (in elite, but not recreational, runners: see the associated Hands On report[6] for a consideration of the benefits of exercise in OA) with development of knee OA and, less so, hip OA. Obesity is a risk factor for the development of OA at all major sites,[19] but has now been elucidated as having an effect mediated by valgus malalignment[20] at the knee, while malalignment itself is an independent risk factor.[21]

Inflammation in/around joint

The most persuasive evidence for the presence of inflammation in OA is the visualisation of inflammation either directly through the arthroscope, or indirectly through modalities of high-resolution musculoskeletal ultrasound or MRI. Pain is associated with synovial hypertrophy or effusion and subchondral changes,[22] which are now regarded as inflammatory,[23] in contrast to other truly structural changes such as cartilage defects. Inflammation is found in the ligaments and McGonagle et al have suggested that entheseal inflammation is an, or even the, initiating factor in OA.[24] Effusion and synovitis are common – the latter is even thought

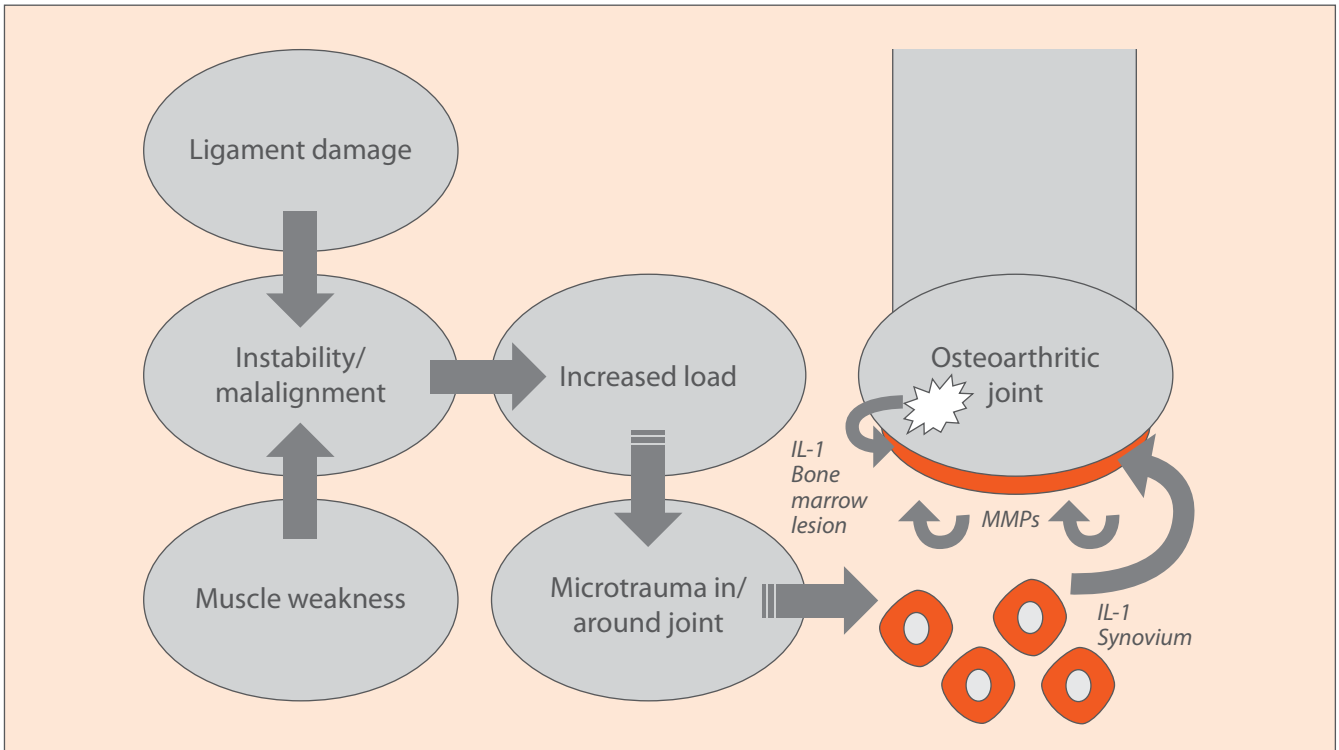

FIGURE 1. A model of OA pathogenesis highlighting link between abnormal biomechanics, inflammation and structural damage.

to be universal from contrast-enhanced MRI series of selected knee OA patients at one centre. Subchondral bone inflammation is one of the most intriguing and probably the most important site of inflammation, however. MRI studies have also shown compartment-specific progression associated with bone marrow oedema lesions.[25] Inflammation demonstrated on arthroscopy[26] or using a highly sensitive C-reactive protein test (CRP)[27] has also been shown to be predictive of progression.

Biochemical mediators

The challenge with studies of biochemical mediators is to understand which are drivers of the disease and which are raised in consequence of disease or repair processes. Putative mediators include interleukins (IL-1β), tumour necrosis factor α (TNFα),[28] MMPs, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), and a disintegrin and metalloproteinase (ADAM), with a proposal that the molecular signature places OA in the same category of disorders as central metabolic syndrome, since it has an active genetic and proteomic profile suggesting inflammation and the cytokine milieu is similarly inflammatory – parallel to that found in the metabolic syndrome.[29] This also links with the observation above regarding excess cardiovascular events. The other key role for mediators is in predicting progression and there is some evidence that serum cartilage oligomeric matrix protein (COMP) and hyaluronan may have a role in predicting incident disease.[30]

Bone response

There are two main aspects to the bone response: subchondral inflammatory changes and hypertrophic response. The former has been mentioned above, corresponds to sclerosis and cyst formation on radiographs, and is the more important with respect to progression. Hypertrophic response leads to osteophytes – visualised as bony spurs on radiographs, but actually representing a flange around the joint, which can be demonstrated with 3-dimensional imaging using high-resolution musculoskeletal ultrasound or MRI, for example.[31] This response does not seem to be strongly associated with either pain or progression.

Scientific basis of current treatment

The current treatment recommendations have been reviewed in the associated Hands On report,[6] based largely on the full guidance in the 2008 National Institute for Health and Clinical Excellence (NICE) OA clinical guideline.[4]

The main goals of future treatment will be to reduce pain and improve function more in a greater proportion of patients and to develop further definitive disease-modifying OA drugs (DMOADs).[33] The three main strategies for slowing disease are:

1. optimisation of the biomechanics
2. prevention of joint failure using agents shown to do so in other types of inflammatory arthritis (disease-modifying anti-rheumatic drugs – DMARDs)
3. interventions targeted at specific points of the pathogenetic pathway: bone, cartilage, ligaments and synovium.

A number of pharmaceutical-sponsored studies are currently taking place looking at specific tissue targets including bone (calcitonin, osteoprotegerin-1), cartilage (aggrecanase inhibition, piascledine: avocado soybean unsaponifiables), ligaments (FGF-18) and synovium (iNOS inhibition).[34]

Another key area of interest is predicting response to treatment. While there is very limited data in this area, one recent study has demonstrated that synovitis on musculoskeletal ultrasound is a biomarker predicting response to guided corticosteroid injection.[35] This confirms that inflammation is important in OA and may lead to a greater focus on studies of established DMARDs as DMOADs. DMARDs have established safety and may be more cost-effective than novel agents.

Surgery for OA

Total joint replacement of the hip and knee is indicated for patients with ongoing pain and functional limitations resistant to pharmacological and non-pharmacological measures. After a difficult start (John Charnley had to remove the first 100 implants as the plastic was too soft) it has become a reliable intervention to improve pain, restore function and improve health-related quality of life.[3,4,36,37] Surgery for severe OA in all other joints can also provide considerable symptomatic relief and functional improvement in appropriately selected patients.[38-40] However, there is a paucity of randomised controlled trial (RCT) evidence on arthroplasty and some of the RCTs for other surgical interventions have delivered surprising results. There is something of a treatment gap in the management of OA between effective non-surgical therapies and arthroplasty

and considerable focus on development of joint-preserving surgical interventions that can bridge this gap.

Case selection

Case selection for surgery in OA is particularly difficult. Guidelines have been developed to summarise available evidence and expert opinion in order to clarify indications for referral and for surgery.[4,37] Key to this difficulty is the considerable variability in reported pain, function and clinical and radiographic findings. As such referral should not be restricted on the basis of radiographic findings. It is important to emphasise that this is true also of scoring systems. A number of scoring systems have been adopted into referral criteria by certain primary care trusts, most commonly the Oxford Hip and Knee Scores. They have not been validated for use in this way, and in knees pre-operative Oxford Knee Score has been shown to correlate poorly with outcome after joint replacement.[4,41] Attempts to delineate cut-offs in levels of pain and dysfunction alone that are an indication for total joint replacement have failed to do so.[42] Decision to refer for surgery is harder when considering patients from wider age ranges, with higher BMI or with more associated co-morbidities. These factors should not restrict referral as these patients can also achieve excellent results, albeit with often substantially increased risks and even greater difficulties in initial surgical decision-making. We don't know exactly what determines good and bad outcomes after joint replacement surgery.[43]

The National Joint Registry (NJR) established in 2003 has become a valuable resource, collecting data on more than 90% of patients undergoing hip and knee replacements in England and Wales. Data collection on ankle replacement has now started; shoulders and elbows are to be included imminently, with efforts to include patient-centred outcomes. 164,000 hip and knee replacements were performed in the last reported year (2009) and this figure is increasing year on year. Of these the indication for surgery was OA in 93%.[3]

Surgical techniques

Hip arthroplasty is the most well-established joint replacement procedure and has now been performed for over 50 years. Alderson recently wrote, 'Few other surgical procedures are likely to have had an impact on pain and disability to a similar extent.'[44] Patient satisfaction rates are consistently reported as greater than 90% and survivorship analysis demonstrates better than 90% revision-free survival at 10 years. Implants are either cemented, uncemented, hybrid (cemented stem and uncemented acetabulum or vice versa) or large-diameter metal-on-metal, 36%, 39%, 15% and 10% respectively in the most recent NJR report.[3] There are theoretical advantages and disadvantages to each technique. From a patient perspective, availability of positive long-term outcome data for a particular prosthesis is perhaps the best guide rather than method of fixation in general when discussing proposed details of surgery.

Metal head and polyethylene cup remains the most commonly used combination of bearing surfaces. Polyethylenes available have much improved wear characteristics and are ultra-high molecular weight, highly cross-linked and sterilised with techniques to minimise degradation. This remains the cost-effective first choice for the lower-demand patient. In the younger, higher-demand patient, alternative solutions have been sought. Ceramics have the lowest in vivo wear rates of available bearing surfaces.[45] First-generation ceramics were brittle with tendency to fail by fracture. Hugely improved production techniques have overcome these concerns. Ceramics are now first choice in the more high-demand patient for most surgeons. Metal-on-metal and ceramic-on-metal are alternatives.

Large diameter metal-on-metal total hip replacements (THR) and hip resurfacings have been the focus of considerable recent attention in medical literature and the wider media. Concerns initially focused on circulating metal ion levels, metal hypersensitivity and the concept of ALVAL (aseptic lymphocyte-dominated vasculitis-associated lesion) or 'pseudotumour' development.[46] More recently emerging registry data on early failure rates with some implant designs has prompted detailed analysis and vigilant follow-up of patients with these prostheses in situ. Theoretical advantages of resurfacing include preservation of bone stock, reduced dislocation risk and improved functional outcomes.[47] Certain resurfacing designs have demonstrated excellent outcomes and survivorship in appropriately selected patients. Others have not, however, and following MHRA advice the articular surface replacement (ASR) prosthesis has been withdrawn amid considerable controversy.[48,49]

Total knee replacement (TKR) recently overtook hip as the most commonly performed primary arthroplasty procedure in the UK. Incidence of TKR doubled

between 1991 and 2000 and had more than doubled again from 2000 to 2010. Unlike hip replacements the established bicondylar designs of current knee replacements have been largely unchanged over this time period. Mobile bearing designs have not demonstrated discernibly improved performance. Expensive computerised navigation techniques to guide surgeons with implant positioning have a role in reducing technical error and in guiding surgery in the very severe cases with extreme deformity. Newer technology is the development of patient-specific, image-based custom instrumentation for knee replacement, based on pre-operative MRI and x-rays: results are awaited.

Unicompartmental knee replacement is an excellent alternative for patients with localised disease and is endorsed in the Osteoarthritis Research Society International (OARSI) recommendations.[37] Objective outcome assessments have shown favourable results in comparison to TKR for medial compartment OA. NJR-quoted increased revision rates in comparison to TKR had prompted caution in more widespread use but subsequently this has been shown to perhaps be misleading.[50] Lateral unicompartmental and patellofemoral replacements are also well established and successful in appropriately selected patients. A compartmental approach to TKR is a consideration for the future.

An effect of the increasing numbers of primary joint replacement procedures, despite improving survivorship, is an increasing revision burden for surgeons. For THR this increased from 9.2% to 10% and for TKR from 4.3% to 5.9% from 2009 to 2010 in England and Wales. This has considerable implications both for focus in surgical research to optimise outcome following revision surgery and for healthcare commissioners to prepare for the increasing demands.

Glenohumeral OA resistant to non-surgical management can be managed successfully with shoulder arthroplasty. Shoulder OA tends to give circumferential cartilage loss with a centred humeral head and a largely intact rotator cuff in contrast to other aetiologies. As such it is well suited to hemiarthroplasty or total shoulder replacement. Both techniques have demonstrated good outcomes with improved pain, motion, strength and function and survivorship greater than 90% at 5 years.[51] Meta-analysis has demonstrated improved functional outcomes and slightly improved survivorship with total replacement compared to hemiarthroplasty.[52] Methods to improve longevity of glenoid fixation are in development. For patients with a deficient rotator cuff, reverse geometry shoulder replacement is becoming increasingly used. Early designs performed poorly. More recent designs are demonstrating encouraging functional results, with mid- to long-term outcome studies still awaited.[53]

OA of the ankle is a less common indication than post-traumatic or inflammatory arthropathy for surgical intervention. Surgical decision-making is between arthroplasty and arthrodesis and careful patient selection is critical as functional outcomes are generally similar. It is accepted that ankle replacement is not without its complications and survivorship has been shown to be 78% at 5 years. Third-generation ankle replacements are however demonstrating improvements in outcomes and recent work has demonstrated improved function in comparison to arthrodesis.[54]

Procedures addressing the treatment gap

Mosely et al published a landmark RCT showing no difference between arthroscopic debridement, arthroscopic lavage or sham surgery. Three further RCTs and a Cochrane review have drawn the same conclusions, hence it is clear that there is no role for arthroscopic lavage or debridement in knee OA.[55] There may be a role for arthroscopic debridement in the presence of mechanical symptoms from degenerate meniscal tears, but further studies are needed.[32,37]

The role of anterior cruciate ligament (ACL) reconstruction in prevention of knee OA is topical. A recent study has demonstrated a unique pattern of OA with increased wear posterolaterally in the ACL-deficient knee.[56] What is not clear is whether all patients with an ACL-deficient knee are at increased risk. A proportion do well with rehabilitation, non-operative management and activity modification initially. Longitudinal studies are ongoing to compare this cohort with a reconstructed cohort, as well as to look at the effect of timing of reconstruction on subsequent OA.

Cartilage regeneration procedures continue to evolve and develop to treat isolated cartilage defects, mainly in the knee. Microfracture has been widely used, but lacks any controlled trial data. This involves penetration of the subchondral bone to allow marrow stromal cells containing mesenchymal stem cells, platelets and other chemotactic factors to collect within the defect and differentiate and produce a fibrocartilaginous repair response. More hyaline-

like cartilage has been achieved using autologous and matrix-induced autologous chondrocyte implantation (ACI and MACI) techniques. This involves harvesting autologous cartilage from the non-weight-bearing area of the same joint, expanding the chondrocytes in vitro and then returning them to the defect. This is potentially a more durable repair.[57] Recent studies have demonstrated functional superiority of chondrocyte implantation versus microfracture at 3-year follow-up.[58] The techniques are promising but are currently only suitable for relatively small discrete lesions, they remain expensive, and results are much better in younger patients.

With current opinion that OA is a pathophysiological response of the whole joint to an abnormal mechanical environment, osteotomy to alter that mechanical environment makes intuitive sense.[59] There is anecdotal evidence, including case series, that osteotomy around the hip and knee can be a successful procedure for young patients with symptomatic OA and may delay progression to joint replacement.[37] In addition, for more isolated areas of cartilage loss amenable to cartilage regeneration procedures, adjunctive osteotomies to offload the damaged area have improved some outcomes.[57] Distraction is another method that has been trialled in order to offload and alter the mechanical environment in osteoarthritic joints in both ankle and knee. Pilot studies suggest that cartilage may be regenerated in the offloaded joint when an external frame is applied for 2 months,[60] but larger and longer studies are needed.

Femoroacetabular impingement is relatively recent terminology for a spectrum of proximal femoral and acetabular dysmorphisms characterised by Ganz.[15] This has been shown to be a common cause of hip pain in young adults and a precursor to hip OA. Broadly, abnormalities are described as cam-type or pincer-type impingement. In practice most patients are on a spectrum between the two extremes. Open and arthroscopic surgical debridement techniques have been developed to remove the impinging bone. Functional outcomes are excellent but long-term studies to assess the role of these techniques in the prevention of subsequent arthritis are awaited. Impingement surgery in the context of established arthritis has been shown to do poorly.[61,62]

Focus on outcomes

In an attempt to aid case selection, research into both what determines outcome following joint replacement surgery and how it is measured are areas of considerable focus. Assessment of pain in OA has moved on from quantification of severity to an evaluation of the characteristics and quality of pain. A variety of new screening tools have been devised to aid the clinician with the aim of identifying different types of pain. It has been shown that ability to pre-operatively identify patients with a tendency towards central pain sensitisation can predict post-operative dissatisfaction.[63] Patient self-reported outcomes via a myriad of different questionnaires are increasingly used to compare pre- and post-operative function following joint replacement. These are validated and useful, but they have been shown to correlate relatively poorly with functional assessment; therefore studies of more objective assessment of function are being performed, including functional gait analysis, pedometry and motion analysis.

Novel cell research

Techniques to improve cartilage defect repair and ultimately develop biologic joint resurfacing for osteoarthritic joints is the focus of considerable research efforts. 'Characterised' ACI is a third-generation modification of the standard technique in which the cells are selected during culture while producing maximal type II collagen and proteoglycan. This technique has shown superior functional outcomes to microfracture in a 36-month RCT.[58]

Autologous matrix-induced chondrogenesis (AMIC) is a new technique which involves piercing the subchondral bone with a standard microfracture technique and then covering the area with a type I/II collagen membrane. This has been shown to increase quantities of type II collagen and proteoglycans with promising early clinical results.

The possibility of using stem cell therapy in the treatment of OA remains an ultimate goal. Mesenchymal stem cells have been used in the repair of isolated cartilage defects with similar results to autologous chondrocyte implantation. They have also been shown to enhance healing of meniscal defects when injected into the knee and to enhance healing of fractures when injected into fracture sites. Stem cell targeting to osteoarthritic cartilage has been proposed as a way of replacing the chondrogenic progenitor cells lost in early OA in order to prevent progression of OA. These studies are yet to be performed.

Being limited to enclosed joints, OA is a disease that is ideally suited to intervention delivered via gene therapy. Genetic modification of therapeutic cells or host tissue to overexpress anabolic factors that can act to prevent progression of the osteoarthritic process or repair cartilage have been studied. Focus has been on TGFβ (important in the development of cartilage) and IL-4, IL-1 and IGF-1 (important in the OA inflammatory cascade), with some encouraging results in vivo and in animal models.[64] These offer exciting potential therapies that need to be developed and then rigorously tested in appropriately designed RCTs to deliver effective treatment options for this increasingly common and important problem.

Conclusion

In conclusion, osteoarthritis can now be more accurately described as a disease of 'tear, flare and repair'. Resources like the National Joint Registry are providing better data on surgical practice and novel treatment strategies are being developed based on our improved understanding of pathogenesis. This is an exciting time to be in osteoarthritis research. Greater collaboration between basic scientists and clinicians, as well as an increasing coordination of strategy across the UK and globally, has the potential to deliver genuine translational breakthroughs in osteoarthritis therapy.

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