REVIEW ARTICLE

RECENT ADVANCES IN OSTEOARTHRITIS

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ABSTRACT

Osteoarthritis (OA) is a very common affliction and is associated with much disability. In the past decade important advances have been made in our understanding and treatment of OA. New technology in imaging and biochemistry have helped towards the identification of prognostic markers of disease and providing sensitive techniques to test the effects of new exciting drugs for intervention. New information regarding the heterogeneity and aetopathogenesis of OA adds to this excitement. It may not be long before we will be in a position to predict the progression of the disease and contemplate intervention with disease modifying agents. This review discusses these latest advances in the study and management of OA.

Keywords: distribution, biochemical markers, imaging, prognosis, intervention

INTRODUCTION

A sad indictment of modern medical thinking is that a chronic non fatal condition like OA has received lower priority than a disease like ischaemic heart disease. OA inflicts upon patients a tremendous life-long burden, which we as members of the wider community cannot afford to ignore as we will have to shoulder its cost eventually.

OA is one of the most common causes of disability in the elderly age group. In the United Kingdom at least 10% of the population suffer symptoms requiring treatment and at least 10% of these sufferers will be severely disabled by it\(^\text{10}\). Research has been difficult because of the lack of sensitive tools with which to study it. It may be asserted that the solution to a problem where the body can no longer repair itself against the tide of time and attrition is surgical replacement. Surgery is a limited resource and is beyond the reach of the majority of the world's sufferers. Moreover, it is invasive, has a definite morbidity and mortality, and even in the best hands, replaced joints have a limited life span.

In the last decade dedicated interest has raised the profile of research in OA. Great strides have been made. We are now in a position where the potential to intervene decisively in this wretched condition may soon be realised. This paper seeks to address those advances that have been made and the potential for future benefit to sufferers world-wide. In this brief review we will consider the latest trends in our understanding of its clinical categorisation and the advances that have been made in radio imaging, biochemistry and molecular biology in the study of OA.

ADVANCES IN UNDERSTANDING

The osteoarthritic diseases are a very heterogeneous spectrum of conditions. They can be described as the final common pathway of processes that lead to joint failure. No one mechanism explains all the processes that occur in osteoarthritic joints. The main common factors in OA are increasing age and female sex though the underlying mechanisms in each joint or groups of joints may be different and separate\(^\text{20}\). Many factors may play a part including genetics, inflammation, injury or trauma, joint mechanics, and so on. Much is made of diagnostic criteria for OA but the value of this when applying it rigidly to a process rather than a disease has its limitations\(^\text{20}\). However, certain patterns of OA can be recognised.

JOINT RESPONSE

The earliest observations about arthritis differentiated the hypertrophic from the atrophic form. It became apparent that the atrophic forms were mainly due to rheumatoid arthritis and inflammatory arthropathies. The individual response to joint insult is a balance of the catabolic versus the anabolic responses (Fig 1). We recognise easily the hypertrophic form of OA with prominent osteophytic formation due to remodelling. There is also the atrophic form classically illustrated by the Apatite Associated Disease (ADA) of the shoulder and the rapidly progressive hip OA. What factor(s) determines the greater of each particular response in any individual is the subject of intense research.

DISTRIBUTION

Dieppe/Cushnaghan hypothesis and evolutionary hypothesis

Certain patterns of distribution in OA are recognised. The polyarticular sporadic form in the elderly is the most common. Whether it should be differentiated from "generalised OA", which was used to describe polyarticular involvement in menopausal women of a much younger age group, is still unclear\(^\text{46}\). In both groups the joints affected include the finger interphalangeal joints, thumb bases, metacarpal-phalangeal joints, knees, spines, and the first metatarsal-phalangeal joints. The joints affected are usually symmetrically involved and the number of joints affected in the elderly is acquired with time, a process described by the Cushnaghan/Dieppe hypothesis\(^\text{33,46}\). The onset...
Fig 1 – Osteoarthritis is a process involving many different influences. The individual joint response is a balance of the anabolic and catabolic processes acting in conjunction with a host of extrinsic and intrinsic factors.

Neuropathy  
Vascular injury  
Subchondral bone collapse  
Bone form (?Deh)  
Cartilage destruction  
Subchondral sclerosis  
Osteophytes

Genetics

Atrophic

Δ

Hypertrophic

Cytokines (IL 1, II 6)  
Synovial inflammation  
Proteolytic enzymes  
TIMP (tissue inhibitors of metalloproteinases)  
Growth factors (IGF-1)

Neuropathy  
Vascular injury  
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Osteophytes

and progression of joint damage in any individual is a function of physiological ageing. Quite another matter is what accelerates this process.

The most consistent observation is that certain joints are particularly susceptible to OA. Hutton was the first to coin the evolutionary hypothesis of under-designed joints(15). The evolutionary process of attaining the upright stance and the prehensile grip conferred great advantages but rendered certain joints susceptible to OA. The evolutionary changes of the hip, knee, vertebral spine and hand provide us with examples of how design and the balance of stress on a joint play their part in the development of OA in man. Thus, the joints of the knee and the thumb base were under-evolved to the tasks that were demanded of them. This is compounded by the longevity of man and, in particular, women in the post-menopausal era. The evolutionary hypothesis predicts which joints in man are prone to failure due to incongruence between joint function and joint design. Recent evidence also suggests that within each joint there are subtle differences implying separate mechanisms. For example, the patello-femoral OA of the knee (POAK) and the medial tibio-femoral OA of the knee (MOAK) have been shown to be different(26), the superior pole as opposed to the medial pole disease of the hip(29) and the thumb base joint and disease of the inter-phalangeal joint of the hand(30).

These observations highlight the complexities of the aetiopathogenesis of OA at different joints. They caution against using simplistic concepts that treat every joint affected by OA as the same. The next section explores various investigative tools that have been used to study OA joints.

INVESTIGATIONS

Radiology

It is now clear that investigation of the knee with the PA radiograph would be incomplete without views of the patello-femoral joint (PFJ) (Fig 2). The skyline view is preferred but the lateral is still useful. Another important growth area is quantitative microfocal radiography (QMR)(9). This technique employs a specific system with a narrow beam allowing greater magnification of the image and clarity with excellent reproducibility. It allows better quantification of individual features of joint. It has greater sensitivity in picking early occurrence and subsequent resolution of rheumatoid erosions. Work by Buckland-Wright and colleagues has combined the resources of QMR with bone scintigraphy, forming a formidable formula to understand the OA process. Unfortunately, this is not a readily available resource and is expensive.

Arguably the best predictor of disease progression available in radio imaging today is technetium pertechnetate scintigraphy. Bone scintigraphy shows up two phases, the early (perfusion phase) and the late (bone phase). Scintigraphy can predict disease progression long before X-ray changes occur(15) (Fig 3). Work is needed to define the exact biology of the different phases of the scan.

CT scanning has a limited use mainly because it has been superseded by Magnetic Resonance Imaging (MRI)(14). Gadolinium scanning of the knee with appropriate software is being developed to quantify joint structures like the synovium, synovial fluid volume and cartilage mass. It has been found that the earliest change appears to be an increase in cartilage signal intensity. Later changes correlate well with pathological changes.

Fig 2 – Plain AP radiograph of a female aged 60 with medial compartment tibio-femoral OA. Features are osteophytosis, joint space narrowing and subchondral sclerosis. There is also lateral displacement of the patellae with osteophytosis suggesting the presence of marked patello-femoral disease as well.

Fig 3 – Technetium bone scintigraphy of knees. The late phase scan shows increase in uptake in both medial compartments. This suggests the presence of subchondral bone changes and osteophytes and would predict a poorer prognosis over the next five years.
(Fig 4). The potential of MRI to detect early change(s) will be its main advantage and it is non-invasive. This has obvious implications in two key areas is assessment of intervention and prediction of outcome. Its main drawbacks are its expense and requirement for skilled personnel. At present, it remains very much a research tool in the study of OA though there are strong advocates for its routine use.

Dual Energy X-ray Absorptiometry (DEXA) was initially introduced in 1987 as a technique to measure bone mineral density in metabolic diseases such as osteoporosis. With improvements in software DEXA is now being used in orthopaedics to monitor prosthesis-fixation and bone lengthening\(^2\). Osteoarthritis is a process involving the subchondral bone, the cartilage, the synovium and soft tissues. DEXA scanning is currently being used to study the role of the subchondral bone in OA (Fig 5). The technique is simple and inexpensive and gives excellent precision with good reproducibility\(^{15,16}\). With radiation exposure a fraction of conventional X-ray, it opens up the possibility of assessing early changes to bone and possibly cartilage, at frequent intervals.

Subtle changes in the cartilage are now being quantified by chondroscopy, a less invasive form of arthroscopy. For the future it may be possible to use scopes with the bore of a needle (needlescopes) to study OA cartilage. Grading systems are currently being refined and there is the potential to calibrate changes seen on the MRI and biochemical markers with gross appearances of the cartilage in humans\(^{31}\).

**SERUM AND SYNOVIAL MARKERS**

By the time the patient with OA presents with joint pain, the disease is often advanced. Moreover, studies on pathological specimens show that the cartilage and joint may be badly affected despite normal radiology. The current goal is to develop practical, inexpensive and minimally invasive tests to detect sub clinical OA and to monitor disease progression.

OA affects two distinct types of connective tissue in diarthrodial joints ie bone and cartilage. In a normal joint the integrity of these tissues is maintained by a stable equilibrium between synthesis of new components and degradation of the old ones. These constituents give rise to a class of macromolecules which indicate bone and cartilage turnover. They are released into the synovial fluid, enter the circulation via the lymphatics and are eventually eliminated from the body by the liver and kidneys. In OA the normally stable equilibrium is disrupted. The measurements of these markers may lend insight to changes in OA joints and provide an adjunct if not alternative mode to the more costly and sometimes invasive imaging techniques. Cross sectional and longitudinal studies have confirmed the usefulness of biochemical markers in OA\(^{18-20}\). Cartilage markers such as keratan sulphate (5D4), chondroitin sulphate (3B3) and collagen propeptides have been measured in serum and synovial fluid\(^{21-23}\). Similarly, bone markers such as osteocalcin and alkaline phosphatase have some disease specificity and appear to correlate with changes in the subchondral bone\(^{24,25}\). We have found that bone specific alkaline phosphatase in synovial fluid reflect bone turnover more accurately than osteocalcin levels (unpublished observation, M Sharif).

The main drawback in the measurement of markers in serum is in interpreting the data as they can be profoundly affected by many variables including age, sex, disease duration and clearance rate (Fig 6). For a review of the pitfalls of serological markers see the article by Brand\(^{26}\). Some of the difficulties associated

**Fig 4 - Unenhanced MRI of OA knees showing cartilage damage and altered signal. Gadolinium enhancement is being tested to quantify the synovium and cartilage mass.**

**Fig 5 - DEXA scanning of knees. This is a novel method of assessing subchondral bone in joints. Improved software and hardware may soon make repeatable measurements of changes in joints a precise and safe science.**

**Fig 6 - Biochemical markers of joint disease. Biochemical markers of cartilage, bone and soft tissue turnover are complex molecules to study and understand. Its full potential is still to be realised in routine use.**
with evaluating serum levels of markers can be overcome by measuring markers in the synovial fluid. Moreover, it may be necessary to assay several markers so that values can be expressed as ratios, eliminating the need to relate markers to effusion volumes. Recently, the role of inflammation in OA has received a renewed life. There is evidence for example that serum hyaluronic acid, a systemic marker of inflammation, has been shown to be raised in OA and in one study predicted disease progression.

Ideally, we need markers that will tell us which individuals are at risk of developing OA and who will progress; just as what the glucose tolerance test is to diabetes and what the log of creatinine clearance over time tells us of impending renal replacement therapy. Presently, this seems far in the horizon but considering the potential of such a tool, it is well worth investing time and effort on. Several predictive markers interpreted together most likely will yield the most information.

FUTURE STRATEGIES
There is a need to improve data collection and patient selection in studies on OA. Refinement of techniques like MRI and DEXA can be used with studies in conjunction with QMR, scintigraphy, chondroscopy and biochemical markers. These techniques need calibrating.

COMPARATIVE ANATOMY
A study of OA in the rhesus macaque (Macaca mulatta) confirmed the presence of osteoarthritis of the distal interphalangeal and to a much lesser thumb base OA. The latter fact may be related to the almost rudimentary opposition and lack of power grip that the thumb in macaques allows. The other fascinating aspect was that rhesus macaques were found to have multiple nodal OA occurring symmetrically as in humans. Work in paleopathology and examination of archaeological specimens provide clues to the antiquity of OA. There is a suggestion that tibio-femoral OA which is common in modern man, was a relatively rare disease in antiquity whereas the patello-femoral joint has been afflicted for longer. If this is true, then it supports suggestions that obesity and lack of physical activity predispose to tibio-femoral OA. These hazards of modern day living are compounded by impact forces induced when walking on concrete surfaces.

Fig 7 - PA X-ray of macaque hands. OA of the DIPJs is present. The distribution of OA in the IPJs follow the pattern seen in man but thumb base disease is rare, suggesting that the human disease is an evolutionary problem.

MOLECULAR GENETICS
Since the discovery of defects in the Col 2A1 gene that predisposes to chondrodystrophic dysplasia and premature OA, molecular biologists have become involved in research in this area. Reports have been sporadic and it is still unclear as to how applicable a very rare genetic defect causing dysplasia in the joints is to the main burden of sporadic OA. Nevertheless the race is on in some centres to find the ‘OA gene’.

INTERVENTION
Just as there are disease modifying drugs for rheumatoid arthritis, it is hoped that soon there will be effective and safe drugs that can be used to retard the progression of OA. At a WHO/LAR meeting, criteria and definitions for each class of drugs, whether they do or do not exist yet were laid out. Terms like Symptomatic Slow Acting Drugs for Treatment of Osteoarthritis (SYMSADOA) and Disease Modifying OA Drugs (DMOAD) are attempts to standardise drug categorisation in intervention studies. There is room for optimism. In a dog model of OA intervention with doxycycline already has shown promise in its ability to halt the progression of disease. It seems to have a cartilage protective effect through its action on protease inhibitors though it may exert its effect on the subchondral bone as well. The results of its use in humans will be much awaited. This adds to the ever growing number of potential disease modifying drugs in OA like hyaluron, anti-IL-1 antagonists like diacerein, pentosan, inhibitors of metalloproteinases, anti-TNF and so the list goes on. Early results with some of the agents have been disappointing but some of the newer agents with the potential to modify OA are being tested in clinical trials. Another interesting recent development has been cartilage transplantation. This idea can be exploited further by using growth factors with cartilage matrix to encourage repair of cartilage tissue.

It must be mentioned that non pharmacological measures are as important. The use of proper heel shock absorption, weight loss in obesity, quadriiceps strengthening, patient education and support about pain and disease can have a significant impact on the outcome of patients with OA.

The seduction of course, in this era of intervention, is to find that elusive early predictor of OA and its severe subsets. This may help justify intervention long before the condition becomes symptomatic. This long-awaited breakthrough if it occurs, will no doubt be a result of a closer than ever synthesis between high tech basic science and the equally important direction from dogged, astute clinical observation.

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REFERENCES
6. Cushnaghan J, Dieppe PA. Study of 500 patients with limb joint