Pathogenesis and management of pain in osteoarthritis

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Summary
The term osteoarthritis describes a common, age-related, heterogeneous group of disorders characterised pathologically by focal areas of loss of articular cartilage in synovial joints, associated with varying degrees of osteophyte formation, subchondral bone change, and synovitis. Joint damage is caused by a mixture of systemic factors that predispose to the disease, and local mechanical factors that dictate its distribution and severity. Various genetic abnormalities have been described, but most sporadic osteoarthritis probably depends on minor contributions from several genetic loci. Osteoarthritic joint damage may be associated with clinical problems, but the severity of joint disease is only weakly related to that of the clinical problem. For this reason the associations and pathogenesis of pain are in as much need of investigation as joint damage. Subchondral bone and synovium may be responsible for nociceptive stimuli, and peripheral neuronal sensitisation is an important feature, and can result in normal activities (such as walking) causing pain. Central pain sensitisation can also occur, and psychosocial factors are important determinants of pain severity. We present a stepwise approach to the management of osteoarthritis.

Introduction
Osteoarthritis is a common disorder of synovial joints. It is characterised pathologically by focal areas of damage to the articular cartilage, centred on load-bearing areas, associated with new bone formation at the joint margins (osteophytosis), changes in the subchondral bone, variable degrees of mild synovitis, and thickening of the joint capsule (figure 1).1 When this disease is advanced it is visible on plain radiographs, which show narrowing of joint space (due to cartilage loss), osteophytes, and sometimes changes in the subchondral bone (figure 2).2 Osteoarthritis can arise in any synovial joint in the body, but is most common in the hands, knees, hips, and spine. A single joint could be involved, but more commonly several joints are affected. This condition is strongly age-related, being less common before 40 years, but rising in frequency with age, such that most people older than 70 years have radiological evidence of osteoarthritis in some joints.3

The clinical problems associated with these pathological and radiographic changes include joint pain related to use, short-lasting inactivity stiffness of joints, pain on movement with a restricted range, and cracking of joints (crepitus). Pain is particularly important, and osteoarthritis is thought to be the biggest cause of the high rate of regional joint pain in older people.4 However, the correlation between radiographic evidence of osteoarthritis and the symptomatic disease is rather weak. This raises issues relating to the definition of the so-called disease and to the extent to which we should be studying the cause of joint damage, or the causes of pain and physical disability in older people.

Scope
The purpose of this Seminar is to focus on three topical, important, inter-related, and controversial aspects of the disorder. First, we consider the relations between joint damage and joint pain, before reviewing some data about the risk factors and pathogenesis for each of these factors, concentrating on progression of joint damage and persistence of pain. We then consider the genetics of osteoarthritis, and the inter-related issue of the phenotypic expression of the disease. Finally, we present some principles of diagnosis, assessment, and management.

Joint damage and joint pain
Radiography has been the main method used to define osteoarthritis for epidemiological purposes. Community-based radiography studies show that this condition is extremely common in older people.5,6 But frequency data vary, partly because of population differences, perhaps also because of the use of different cut-off values. Radiographs have provided an important source of information on the distribution and extent of osteoarthritis in older people, and have been used to describe the changes in bone, subchondral bone cysts, and focal area of extensive loss of articular cartilage.

Figure 1: Slab radiograph of (A) normal and (B) osteoarthritic femoral head
Radiograph of osteoarthritic joint shows marginal osteophytes, change in shape of bone, subchondral bone cysts, and focal area of extensive loss of articular cartilage.

Search strategy and selection criteria
We searched MEDLINE and Embase, combining the term "osteoarthritis" with "pain", "genetics", "genes", "management", or "treatment".

Figure 2: Radiograph of osteoarthritic joint shows marginal osteophytes, change in shape of bone, subchondral bone cysts, and focal area of extensive loss of articular cartilage.
points to define the presence or absence of osteoarthritis, and because problems exist with the sensitivity of the radiograph. The use of MRI and arthroscopy make it clear that early osteoarthritic changes are not apparent on the radiograph, but these techniques cannot easily be used in population studies.

Joint pain is very common in older people in all communities. Widespread chronic pain is present in some 10-15% of the UK population at any one time. Regional joint pain is even more common, some 25% of the population reporting knee pain or back pain in cross-sectional studies. However, there are no valid criteria for epidemiological use that allow us to say which people with regional joint pain have osteoarthritis. The only clinical criteria for this condition are those produced some years ago by the American College of Rheumatology, but they were derived from data that compared hospital patients with a diagnosis of osteoarthritis with those who had inflammatory joint disease; these criteria are therefore of limited value and are unlikely to be applicable to community-based epidemiological studies. But nowadays the disease-based, reductionist model of health is pre-eminent, so it is not surprising that the high frequency of pain in joint sites that are commonly affected by osteoarthritis has led to the assumption that this disorder is the sole cause of such pain. Is this assumption justified?

In the 1960s, John Lawrence and colleagues showed that people with radiographic evidence of osteoarthritis were more likely to have joint pain than were those without any such changes, but also that severe radiographic changes could be present with few or no symptoms. More recent studies have confirmed and extended these findings. It is clear that radiographic evidence of joint damage predisposes to joint pain, but that the severity of the joint damage on the radiograph bears little relation to the severity of the pain experienced.

Joint damage and joint pain are both common: many people are susceptible to one or both (through either the genetic or environmental risk factors outlined below). But there are few data about the incidence (rather than prevalence) of either event, and it is unclear what causes the conversion from non-disease to disease (Figure 3).

Risk factors associated with joint damage and its progression
Problems with the definition of osteoarthritis, and the populations used to study it, affect the data available about risk factors. Many data about the risk factors for joint damage are available from community studies that have generally used the Kellgren and Lawrence X-ray grading system to define osteoarthritis. In addition to age, the other main risk factors for radiographic changes include family history, some inherited and developmental conditions that affect bone or joint growth or shape, joint injuries, selected activities (such as farming and hip osteoarthritis) and obesity (Figure 4). However, the balance of risk factors varies according to joint site. For example, obesity is a very strong risk factor for knee disease. Being obese also increases risk of both hip and
hand disease (suggesting that the issue might be more than simply mechanical), but the odds ratios of these associations are much smaller from those for knee osteoarthritis. Similarly, the female to male ratios differ at different joint sites: knee disease has a much stronger female bias than hip disease, for example.

There is some evidence that the risk factors for progressive joint damage are different from those of incident osteoarthritis, although the problems with definitions and cut-off points mentioned make it difficult to make this distinction. Bone density is a risk factor of interest in this regard. Some data suggest a negative association between osteoarthritis and osteoporosis, even after correction for body-mass index, although this association is disputed. It has also been suggested that although osteoporosis might protect somewhat from getting osteoarthritis, having osteoporosis greatly increases the chance of progressive joint damage if one is already osteoarthritic.

Osteoarthritis has generally been thought of as a progressive condition. Several studies suggest that this is not necessarily the case, and that the group mean rate of progression of joint damage from earlier studies is affected by a few fast-progressing individuals. These data are consistent with the fact that only a small proportion of the huge numbers of people in the community with osteoarthritis ultimately need joint replacement. This point is important for clinicians, because they can reassure their patients with early osteoarthritis that they are unlikely to have progressive disease.

The pathogenesis of joint damage
The tissue that has attracted most attention in relation to the pathogenesis of this disease is articular cartilage, largely because of the striking changes in this tissue in advanced osteoarthritis (figure 1). The surfaces of joints are covered by a thin layer of articular cartilage resting on subchondral bone. Cartilage does not have nerves or blood vessels, whereas both are plentiful in bone. Healthy joint cartilage distributes static and dynamic joint loading and decreases friction. Sparsely distributed cartilage cells maintain a cartilage matrix rich in collagen and proteoglycans. The quality of this matrix is critical for maintaining the functional properties of the cartilage. Changes in the joint cartilage associated with osteoarthritis include gradual proteolytic degradation of the matrix, associated with increased synthesis of the same (or slightly altered) matrix components by chondrocytes. These events at the molecular level result in early morphological changes—cartilage surface fibrillation, cleft formation, and later loss of cartilage volume.

Concomitant events in bone are less well understood, but include the development of osteophytes at the joint margin, through ossification of cartilage outgrowths, and major changes in the vascularity and turnover of the subchondral bone. Subchondral bone changes could be an important part of the pathogenesis of progressive joint destruction, partly because the bone has far greater ability to repair, adapt, and change the shape of the joint than cartilage; and there might be an association between progression and osteoporosis, as mentioned. Whether events in cartilage precede those in bone, are concomitant with them, or whether subchondral bone changes can actually cause early cartilage damage is uncertain.

Cytokines and other signalling molecules released from the cartilage, synovium, and bone affect chondrocyte function. Osteoarthritis has traditionally been regarded as non-inflammatory arthritis, but improved

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Figure 4: Schematic representation of relations between environmental and endogenous risk factors for joint damage, osteoarthritis, and joint pain, and their consequences.

Figure 5: Pathogenesis of joint pain in osteoarthritis. Note opportunities for sensitisation and modulation of nociceptive input at several levels.
The pathogenesis of joint pain

Cartilage is aneural, so whatever its role in the pathogenesis of joint damage, it cannot be the tissue that directly generates pain. By contrast, subchondral bone, periostium, synovium, ligaments, and the joint capsule are all richly innervated and contain nerve endings that could be the source of nociceptive stimuli in osteoarthritis. Imaging studies at the knee joint have shown a correlation between pain and both synovitis and subchondral bone changes, suggesting that these two tissues could be sources of pain in osteoarthritis. Normal joint tissues seem to be quite insensitive to pain generation, presumably because a low pain threshold would result in all normal movements being painful. However, some evidence indicates that peripheral pain sensitisation is a feature of the osteoarthritic joint, perhaps mediated by nerve growth factors or cytokines. In addition to peripheral pain sensitisation, central pain sensitisation at the spinal or cortical level can occur in osteoarthritis. Finally, the experience of pain will be modulated by psychological, social, and other contextual factors (figure 5). Pain in osteoarthritis, therefore, could be due to local and central sensitisation of pain pathways resulting in normal stimuli becoming painful. Recent data on pain indicate that we might also need to consider reverse causality, since experimental data suggest that neurogenic inflammation can contribute to joint damage (figures 4 and 5) and, as noted above, inflammation might be an important feature of the process of osteoarthritis. Pain is accompanied by local production of substance P and cytokines that can interact with inflammation pathways and thereby make a secondary contribution to joint pathology.

In summary, it is clear that any simple unitary concept about the link between joint damage and symptoms in osteoarthritis is untenable. We are faced with a complex interaction between local events in the joint, pain sensitisation, the cortical experience of pain, and what people are doing in their everyday lives. Context (psychosocial, economic and other factors) will be everything in these complex interactions.
Phenotypes, genotypes, and classification

The spectrum of joint problems and symptoms experienced by people with so-called osteoarthritis is very wide. Many have suggested that this condition is a group of disorders with a similar pathological endpoint, rather than a single disease entity, and many attempts have been made to subdivide osteoarthritis by the number and distribution of joints affected (generalised or localised osteoarthritis) or the presence or absence of any obvious cause (primary or secondary osteoarthritis).

Debate has raged for years about the existence of the specific disease entity of generalised, inflammatory or erosive osteoarthritis (figure 6), and the question remains unresolved.34-48 So-called lumpers consider this condition part of the continuum of osteoarthritis; splitters think of it as a separate entity. Improved understanding of the disease means that the common classification into primary and secondary cannot be maintained. Osteoarthritis is a multifactorial disease with genetic and environmental determinants. All cases are probably affected by both genetics and environment, with a continuous distribution between the extremes of predominantly genetic or predominantly environmental. For example, the risk of post-traumatic osteoarthritis after a meniscal injury of the knee is strongly affected by a family history of knee osteoarthritis than was previously thought.15 Among the relevant genes are those coding for molecules in the cartilage matrix such as collagen types II, IX, and XI, COMP, and matrilin-3.

More recent work suggests that variations in the genes for molecules of joint signalling or differentiation pathways are also associated with osteoarthritis. For example, functional variants within the gene for secreted frizzled-related protein 3 are associated with hip osteoarthritis in females. This protein is involved in the Wnt pathway, which is critical in skeletal and joint patterning in embryogenesis, and which might also be a determining factor of mature adult bone mass.

Many but not all genetic variations or mutations are associated with variable expression of the phenotypes spindlyophipphysal dysplasia (SED) or multiple epiphyseal dysplasia (MED). Only few of the identified loci and genes have been confirmed in more than one population, and so far each identified gene variation explains only a small proportion of all osteoarthritis. Cross-population comparisons are often hampered by use of different phenotype definitions. Much work on genetics has so far focused on the concept of one joint, one gene, by which it is assumed that a single haplotype, polymorphism, or mutation is linked to an increased risk for the disease in the hand or the hip, for example. It is unclear to what extent this concept holds true, or if specific genomic variations are pleomorphic and variably influence development of osteoarthritis in more than one anatomical site. For either scenario, environmental effects might be key.

Continued analysis of shared and non-shared environmental effects, and of their interaction with each other and with genetic factors, is important for our understanding of osteoarthritis. We need to understand the role of a permissible environment for initiation and phenotypic expression of the genotypic variations in the disease. Doing so should help identify high-risk groups and determine the role of variations in the genome associated with osteoarthritis.
Panel: Common clinical features of osteoarthritis that allow a bedside diagnosis to be made

- Increased age: It is unusual to develop the disease before age 40 years.
- Pain: Use-related joint pain, relieved by rest, is one of the cardinal features of the disease; in more advanced cases rest pain and night pain can also develop.
- Stiffness: Most people with symptomatic osteoarthritis of large joints experience short-lasting inactivity stiffness or gelling of joints, which wears off in a few minutes with use.
- Reduced movement: The range of movement of the joint is often restricted, and there is generally pain on movement, particularly at the end of the range.
- Swelling: Many osteoarthritic joints develop palpable firm swellings at the joint margin due to the formation of osteophytes; some have minor soft tissue swelling due to secondary synovitis.
- Crepitus: Osteoarthritis joints often crack or creak on movement.

Diagnosis and assessment

The main clinical features of the disease make it, in general, an easily recognised clinical entity (panel). In practice, the most common clinical problem is differentiation of painful osteoarthritis from three other common causes of regional or generalised joint pain in older people: referred pain, periarticular (soft-tissue) conditions, and somatisation (regional pain in the absence of any local pathological cause). Pain in lower limb joints can be referred from the spine, or from the joint above (hip disease causing knee pain is a classic case). Periarticular pain problems are common in all ages, and can accompany osteoarthritis or mimic it; common examples are trochanteric bursitis causing apparent hip pain and anserine bursitis causing apparent knee pain. Additionally, somatisation is a common cause of musculoskeletal pain, especially back pain, and clues to its presence are provided by so-called yellow flags.** A careful history and examination should allow the clinician to make these diagnoses accurately.

Gauging the severity of osteoarthritis involves assessment of both joint and patient. This assessment may be done in the clinical setting in support of diagnosis, treatment decision, or evaluation of treatment response. The clinical examination of the osteoarthritic joint can be helpful in assessing the extent of joint damage, such as deformity and instability, but the reproducibility of findings is low.¹¹ Radiographic examination is often done in support of the clinical diagnosis of osteoarthritis, but in view of the poor correlation between clinical problems and pain, the value of such an examination is debatable. The radiograph can do harm, because it may convince a person that they have degeneration of their joints, when in fact the radiographic changes are irrelevant to their problems. However, such examinations with standard methods provide important information for the surgeon if an intervention such as osteotomy or joint replacement is being considered.

Many disease-specific questionnaires have been developed and validated for standardised assessment of symptoms, function, and disability in osteoarthritis.¹² Some of these instruments are useful in a routine clinical setting, and might also be used for cost-utility estimates. Other instruments are more extensive and only appropriate for research. The validity of any instrument for the particular patient group (and joint) to be studied must be considered before making a choice. For example, the addition of new modules in the questionnaire "knee injury and osteoarthritis outcome score" (KOOS)²⁶ to an already well tested instrument such as the Western Ontario and McMaster Universities osteoarthritis index (WOMAC)²⁷ improved its responsiveness when applied to patients with knee osteoarthritis, who have higher expectations and are more active than those for which WOMAC was originally designed (www.koos.nu).

Principles of management

Several reviews and guidelines on the management of osteoarthritis exist, based on evidence from trials about...
the effectiveness of the various interventions available. We do not intend to review these data, but rather outline some general principles that we believe are important for good management of people with this condition.

Although symptomatic osteoarthritis is very common in the community, much of it is mild, and progression to severe disease is fairly uncommon. Moreover, it is clear that many elderly people regard musculoskeletal aches and pains and stiffness as a normal part of the aging process, rather than a disease. Many never seek medical help. We believe that it is important not to overtreat those who do seek help and advice, and that it is inappropriate to medicise most of those with mild osteoarthritis.

Having said that, many of those who do consult a doctor lead lives that are disrupted by the pain, disability, and distress that accompany their osteoarthritis. It is important that their management centres around a careful assessment of the severity of those patient-related outcomes and not of the severity of joint damage (unless orthopaedic surgery is being considered).

Figure 1 presents a sequential, pyramidal approach to the management of osteoarthritis. All patients should be given general advice about the disease, lifestyle alterations that might reduce symptoms, the need to keep fit and active, and the need to lose weight if they are obese. Referral to allied health professionals can help with delivery of educational and exercise-based interventions, although more and better research is needed about these modalities of treatment, which have not always produced beneficial effects in previous trials.

Additionally, all patients should be encouraged to take control of the condition themselves through self-help measures with proven effectiveness, such as use of simple analgesics and topical agents as well as some nutraceuticals. Only if these measures fail should interventions that require medical supervision, such as non-steroidal anti-inflammatory drugs, physiotherapy, and the use of aids and appliances be considered. Towards the top of the pyramid, for those in whom other measures have failed, are the more invasive interventions. For those with severe osteoarthritis, joint replacement is very effective.

One of the major problems with the practice of evidence-based health care for people with osteoarthritis is that the evidence only concerns single interventions, whereas in practice combinations of different interventions and packages of care involving a mixture of pharmaceutical and non-pharmaceutical treatments are used. We believe that such packages can be very helpful for people with symptomatic osteoarthritis, but this notion remains unproven.

Given the huge economic and personal burden of osteoarthritis, and the fact that it is the main cause of the increasing need for joint replacements, we need to consider prevention. Some of the major risk factors for joint damage are potentially modifiable and, in theory, the rate of obesity and joint injury could be reduced. However, such reductions are unlikely to happen; indeed, both obesity and injury seem to be on the increase, despite knowledge that they are detrimental to health.

Conclusions
Osteoarthritis is an increasingly important public-health problem. Over recent years good progress has been made in our understanding of many of the associations and pathogenic pathways responsible for both the pain and joint damage. As a result, we can develop theoretical strategies for primary prevention of joint damage, through reduction of obesity and joint trauma in particular, but these strategies seem unlikely to decrease osteoarthritis in the short term. Therefore, more research is needed about secondary prevention of progressive joint damage and about control of pain.

References


