Osteoarthritis

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Abstract

Osteoarthritis (OA) is the most common form of joint disease, and its impact is set to grow as the prevalence of obesity rises and our elderly population increases. Many clinicians regard OA as simply a disease of 'wear and tear', and by implication one in which disease modification is not possible. Such prejudices have led to significant academic apathy in this disease, reflected not only in our poor understanding of disease pathogenesis, but also in the failure to classify the disease with greater precision, and to develop sensitive tools for diagnosis and prognostic assessment. The identification of key degradative enzymes in cartilage and the use of mouse models to study disease pathogenesis have greatly changed our outlook in recent years. Evidence-based management of the condition is outlined in international guidelines: education, weight control/loss and exercise (general, joint-specific) are core interventions. Analgesia and non-pharmacological and surgical approaches that favourably affect joint biomechanics are used for treating painful OA unresponsive to core interventions; there are no disease-modifying OA drugs. Ultimately, this disease remains the most common reason for total joint replacement. The next decade is likely to see significant advances in our understanding, and treatment, of this condition.

Keywords Aggrecanase; articular cartilage; diagnosis; hand; knee; mechanical injury; MRCP; osteoarthritis; tests; treatment

Introduction

Osteoarthritis (OA) is the most common form of joint disease, estimated to cost the equivalent of 1–1.5% of the gross domestic product of developed countries. It is characterized by a loss of articular cartilage, an avascular and aneural tissue that overlies the ends of bone at synovial joints, and changes in the other joint tissues that contribute to disease expression.[1]

Pathology

Cartilage is uniquely adapted to perceive and respond to mechanical stress through an elaborate, organized extracellular matrix made up of the proteoglycan aggrecan and type II collagen. Chondrocytes, which are the only cells in cartilage, are responsible for maintaining the matrix during life. Ultimately, these same cells are probably also responsible for making the degradative enzymes that destroy the tissue in disease.

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Key points

- Osteoarthritis (OA) is a highly prevalent condition that affects the axial skeleton and peripheral joints
- Diagnosis is clinical — X-ray features can be absent in early disease
- Education, weight loss and exercise are important first steps in management
- Future research directions include better understanding of the role of surgical procedures, and development of therapeutic targets aimed at mechano-sensing pathways in joint tissues, promotion of intrinsic tissue repair, and identification of prognostic and diagnostic biomarkers

Loss of articular cartilage occurs initially at the articulating surface and then spreads through the matrix down to the subchondral bone (Figure 1). Other changes that occur in the tissue include patchy loss of aggrecan, and clustering and clonal expansion of chondrocytes. Within the joint, there is also sclerosis of the subchondral bone, bony expansion with osteophyte formation and (usually episodic) synovitis.

Cartilage loss frequently precedes the development of pain, which explains why patients often present with advanced joint degeneration. Pain can arise from several of the diseased tissues of the joint, including bone, synovium or other peri-articular structures such as entheses, bursae or tendons. The damaged articular cartilage also produces factors, including nerve growth factor, that can sensitize local pain fibres. Chronic pain, resulting from local sensitization of nerve fibres and central nervous system changes, is common over time.

Aetiology

Traditionally, OA has been designated as either primary or secondary, based on the presence or absence of a known predisposing factor or factors. In practice, it is almost always possible to identify such factors in patients with disease, even though these can be multiple low-impact factors such as family history, obesity and age. Abnormal mechanical load is the most important of these.

Mechanical load

Irrespective of how the disease is classified, the unifying aetiological factor in development of OA is mechanical load — either abnormal load on a normal joint, or normal load on a joint that has lost its mechanoprotective mechanisms (Table 1). This is perhaps most clearly illustrated in young individuals who have sustained destabilizing injuries to the joint (e.g. meniscal or anterior cruciate ligament injuries). They exhibit an OA risk of approximately 50% within 10 years of injury. It is also the case that repetitive low-impact injuries, often occupational, are strongly associated with disease. Likewise, malaligned and misshapen joints are at increased risk of disease.

Conversely, offloading a diseased joint can halt disease progression, as seen in individuals who have sustained a

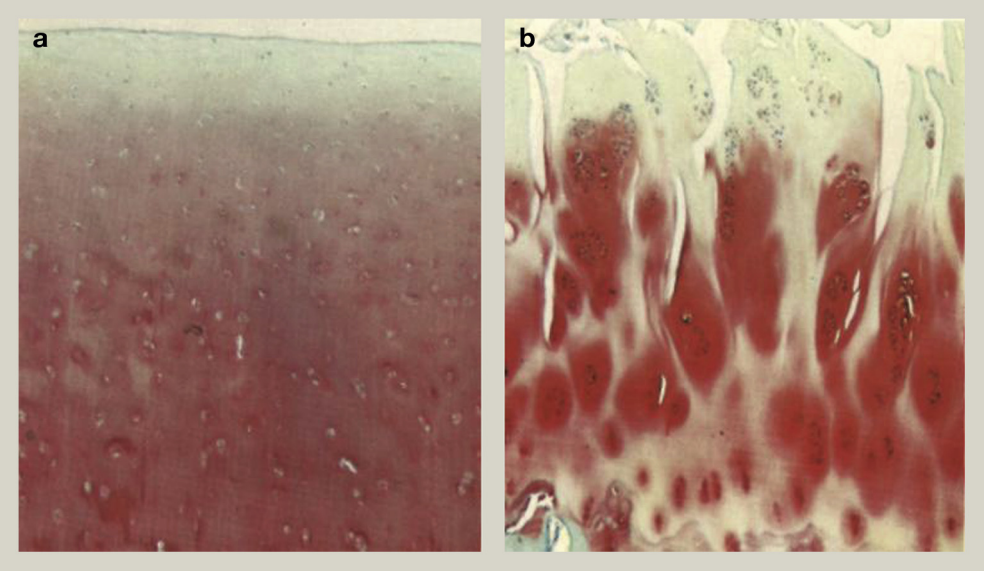

Figure 1 (**a**) Normal and (**b**) osteoarthritic human cartilage stained for proteoglycan (red). Note patchy loss of proteoglycan, tissue fibrillation and clustering of chondrocytes.

Evidence for mechanical factors in OA aetiology

Increased disease by increased load	Increased disease by loss of joint mechanoprotection	Reduced disease by mechanical joint offloading
Overuse (e.g. cotton pickers' (hand), coal miners' (back), farmers' (hip) OA)	Acute destabilizing injuries (e.g. cruciate/ meniscal tears)	Polio and cerebrovascular accident patients have reduced disease on the immobilized side
Obesity	Loss of gait reflexes with age	Disease arrest following high tibial osteotomy
Acute articular cartilage trauma (e.g. intra-articular fracture)	Chondrodysplasias (weak cartilage matrix)	Disease modification following surgical joint distraction
Joint malalignment	Joint damage resulting from previous inflammatory arthritis	Animal are protected from experimental OA with joint immobilization
	Loss of joint support through muscle weakness (e.g. age)	

Table 1

cerebrovascular accident or had polio. Therapeutic approaches to offload the diseased joint, for example high tibial osteotomy or joint distraction (where an external fixator is placed across the joint for a period of 3 months), show good symptomatic responses and might be disease-modifying.

Other important aetiological factors then contribute to the expression of disease and presumably explain why disease is highly heterogeneous and of unpredictable course. Some of these are discussed further below.

Age

Age is likely to contribute to disease risk by a number of mechanisms. Aged joints often exhibit mechanical failure; meniscal failure is evident in 40% of 'age-related' OA in the absence of a history of acute knee trauma. Moreover, loss of muscle strength and reflexes with age suppresses normal mechanoprotective gait responses. It is generally accepted that aged cartilage is more susceptible to degradation, caused in part by a reduction in new matrix synthesis, as well as an increased activation of degradative pathways. Ageing also leads to a failure to clear damaged cells that accumulate in tissues, causing release of reactive oxygen species and tissue damage. Such mechanisms have been observed in joint cells.

Obesity

Increased mechanical load on the joint is one obvious consequence of obesity, as is poor muscle tone leading to loss of joint protection. In addition, adipocytes secrete inflammatory cytokines (adipokines) that can directly drive matrix degradation. Individuals with obesity have higher concentrations of circulating inflammatory response proteins and are at increased risk of metabolic syndrome, which is also associated with OA (see below).

Inflammation

The precise role of inflammation in disease is unclear. Synovitis is invariably present in joints with established OA, but whether it is a bystander or contributes to matrix turnover is unknown. The presence of synovial inflammation on imaging is associated with pain, and has been reported to be associated with progression of the disease. However, neither animal studies nor clinical trials have so far supported anticytokine targeting strategies in OA.

Genetics

From twin studies, heritability in OA is calculated to be around 60%. Recent studies have determined that OA is highly polygenic –