Osteoarthritis

Definition: osteoarthritis from Merriam-Webster's Collegiate(R) Dictionary

(1878) : arthritis marked by degeneration of the cartilage and bone of joints
os•te•o•ar•thrit•ic \-thri-tik\ adj

Summary Article: Osteoarthritis from Encyclopedia of Life Sciences

abstract
Osteoarthritis is a pathological condition of articular cartilage and its underlying bone associated with biomechanical abnormalities and secondary inflammation. These changes result in cartilage loss, subchondral sclerosis, cyst and osteophyte formation, and the clinical sequelae of pain, swelling, deformity and loss of motion in affected joints.

keywords
ageing
articular cartilage
cartilage transplantation
osteoarthritis
total joint replacement

Introduction
Osteoarthritis is the most common cause of musculoskeletal pain and disability. It is a progressive disorder of unknown aetiology with characteristic clinical, radiographic, morphological and metabolic features. The prevalence increases with age, and osteoarthritis can generally be considered a disease of middle to late adulthood. Classically, the osteoarthritic process appears to be initiated by biomechanical abnormalities with a secondary inflammatory component. Thus, preventive measures currently centre around weight loss, activity modification and surgical procedures to correct or compensate for altered joint mechanics or to resurface affected joints or portions of joints. Once osteoarthritis develops, antiinflammatory medications may provide symptomatic relief but, to date, claims of disease modification have been unsubstantiated. In endstage disease, the motion and function can be salvaged by total joint replacement. Continued research into chondroprotective agents, drugs that can arrest and reverse the disease process, identification of genetic factors, and articular cartilage regeneration may eventually lead to a cure for this disabling condition.

Frequency and Clinical Importance
Osteoarthritis is a major public health issue, especially for ageing populations. Based on radiographic evidence, studies have shown that the percentage of people with osteoarthritis of at least one joint increases dramatically with age from less than 5% of those aged under 25 years to more than 80% of
people older than 75 years. In the Framingham Osteoarthritis Study, new radiographic signs of knee osteoarthritis developed in 2% of the cohort each year, with the incidence in women nearly twice that of men. Analysis of patients in a health maintenance organization yielded an age- and sex-standardized incidence rate for hand osteoarthritis at 100 per 100 000 person-years, for hip osteoarthritis at 88 per 100 000 person-years and for knee osteoarthritis at 240 per 100 000 person-years.

The economical impact of osteoarthritis is substantial and is expected to increase as the population ages. In 1994, the average cost of a total knee replacement in the United States was close to $30 000. In 1997, approximately 500 000 primary total hip and knee replacements were performed in the USA. Most of these patients suffered from endstage osteoarthritis. Millions more within the United States suffer from lesser stages of osteoarthritis which contribute to loss of independence, disability, chronic pain and consumption of medical resources at high cost to both the individual and society.

Pathophysiology of the Disease

Detailed studies on the structural and metabolic changes associated with osteoarthritis have not yet yielded a definitive aetiology for this degenerative process. Epidemiological information, clinical studies of patients with altered joint mechanics, and animal models of osteoarthritis point towards a strong mechanical component in classical osteoarthritis. A small subset of patients with metabolic disorders, chondrolysis from infection, or a more generalized pattern of osteoarthritis appear to develop the disease through altered tissue biomechanics. While the earliest signs of the disease are more apparent within the articular cartilage, abnormalities of the subchondral bone are integral to the pathological changes typical of osteoarthritis. Inflammatory changes are not apparent in early osteoarthritis.

Risk factors

Advancing age is the strongest risk factor for the development of osteoarthritis. Age, however, is not the cause of osteoarthritis. There are old joints without osteoarthritic changes and young joints devastated by endstage osteoarthritis. Other major risk factors include obesity, injury, joint dysplasia and overuse. Genetic factors are under active investigation and will almost certainly be found to play a role in determining cartilage resiliency, response to noncatastrophic injury and longevity.

Excess body-weight increases load across weight-bearing joints and is strongly associated with osteoarthritis. Initiation of the osteoarthritic process is thought to occur when the unit load applied to the joint overwhelms the articular cartilage. In healthy joints, the average unit load is approximately 25 kg cm$^{-2}$, a value remarkably constant for different animal and human joints suggesting a narrow tolerance for abnormal loading.

In addition to increased force magnitude from excess body-weight, catastrophic loading may also occur through injury and through cumulative high-frequency use in activities translating multiples of body-weight across the joint. Athletes participating in contact sports have a higher incidence of osteoarthritis than endurance athletes. The specific joint involved also varies based on athletic and occupational loading patterns. One study compared the prevalence of knee osteoarthritis among former soccer players, runners, weight-lifters and rifle shooters. Radiographic signs of knee osteoarthritis were found in only 3% of the rifle shooters. The incidence in runners was nearly five times that of rifle shooters. Soccer players and weight-lifters had close to ten times greater incidence of knee osteoarthritis than rifle shooters. The increased risk for osteoarthritis among weight-lifters was due in part to high body mass, while that of soccer players was related to a high incidence of knee osteoarthritis.
injuries. Soccer players exhibited the highest rate of tibiofemoral arthritis, whereas the patellofemoral joint was most frequently involved among weight-lifters.

Anterior cruciate ligament (ACL) tears, meniscectomy and osteochondral defects are examples of common knee injuries associated with the development of premature osteoarthritis. Existing animal monoarticular models of osteoarthritis such as the Pond-Nuki dog model using ACL transection and sheep meniscectomy models capitalize on the relationship between knee instability and joint incongruity to induce osteoarthritic changes. Exercise models such as the Wistar rat strenuous running model of distance-dependent osteoarthritis demonstrate that repetitive overloading and presumed chronic microtrauma may also damage the joint. See also Biomechanics: Principles

Spontaneous polyarticular osteoarthritis has been found in several strains of mice, guinea-pigs, dogs and primates, suggestive of genetic components to the pathogenesis of osteoarthritis. In humans, primary generalized osteoarthritis is found in middle-aged women and is characterized by symmetrical joint involvement. A single mutation substituting cysteine for arginine at position 519 of the type II procollagen gene has been identified in this disorder. Other metabolic defects known to result in early osteoarthritis that is frequently bilateral and symmetrical include haemochromatosis and ochronosis. Patients with acromegaly are also prone to premature polyarticular osteoarthritis. Reports of familial aggregation of osteoarthritis from cohorts of healthy individuals drawn from community settings lend support to the presence of genetic factors in the pathogenesis of osteoarthritis.

Structural changes of osteoarthritis

Articular cartilage is a connective tissue with a distinct functional structure that allows it to serve as a durable, low friction, material designed to withstand a lifetime of load-bearing and motion. The tissue is composed primarily of extracellular matrix maintained by highly differentiated mesenchymal cells known as chondrocytes. These chondrocytes occupy less than 10% of the tissue volume in adult articular cartilage. The extracellular matrix is composed primarily of water, type II collagen and the proteoglycan aggrecan, with water accounting for 65-80% of the tissue wet weight. Other collagens, proteoglycans, cartilage oligomeric protein, enzymes and other classes of molecules such as lipids and glycoproteins of as yet incompletely elucidated significance are also present within the matrix.

The matrix and cells follow a precise architecture created during organogenesis. Four distinct zones have been described: (1) the superficial zone, (2) the middle or transitional zone, (3) the deep or radial zone, and (4) the zone of calcified cartilage.

The superficial zone (lamina splendins) functions as a gliding surface. It is characterized by thin collagen fibrils which are parallel to the surface. The proteoglycan content is low. Chondrocytes in this zone are thin and longitudinally oriented.

In the middle or transition zone, the chondrocytes assume a rounder shape. The collagen fibres are thicker than that of the superficial zone and are obliquely oriented with respect to the articular surface.

The thickest collagen fibres are found in the deep zone where they extend vertically from within the deeper calcified zone to align with the oblique fibres of the transitional zone and form arches under the gliding surface reminiscent of cross-vaults in a Gothic cathedral. The chondrocytes are arranged in a columnar fashion. Large aggregating proteoglycans are packed within this collagen framework.

Chondrocytes in the deep zone are metabolically active, producing both extracellular matrix
components and degradative enzymes.

This unique architecture confers many of the mechanical properties to the cartilage. The surface layer with its dense collagen fibres parallel to the surface acts in combination with the lubricating glycoproteins to create a frictional resistance five times less than that of ice on ice. Moreover, the proteoglycan-rich central areas with their negatively charged side-chains imbibe water and, when compressed within the collagenous arches, provide a 'shock absorber' function to the matrix.

The tidemark, a cell-free line that appears as a wavy blue line on haematoxylin and eosin-stained histological sections, separates the upper three zones from the zone of calcified cartilage. Chondrocytes of the calcified zone are pyknotic and surrounded by matrix encrusted with calcific salts. This zone appears to separate cartilage from bone.

### Osteoarthritic articular cartilage

The spectrum of structural changes to normal articular cartilage in osteoarthritis ranges from subtle surface irregularities and alterations in matrix staining detectable only by microscopic examination to complete loss of cartilage with exposure of sclerotic, eburnated, subchondral bone. Variations of the Outerbridge classification (Table 1) are commonly used to grade the degree of degeneration visible on gross or arthroscopic inspection.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Softening, small blisters</td>
</tr>
<tr>
<td>II</td>
<td>Fibrillation, partial thickness</td>
</tr>
<tr>
<td>III</td>
<td>Fissures and clefts, full thickness</td>
</tr>
<tr>
<td>IV</td>
<td>Exposed subchondral bone</td>
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The earliest histological changes include surface irregularities and superficial fissuring indicating disruption of the collagen framework. This may be accompanied by subtle decreased Safranin O or Alcian blue superficial matrix staining from proteoglycan loss. As the disease progresses, superficial zone fragmentation and fissuring extends into the transitional zone. Depletion of proteoglycans can be observed through progressive loss of matrix metachromatic staining from superficial to deeper layers, and then from interterritorial regions to the territorial matrix enveloping chondrocytes and chondrocyte clones. As joint surface fragmentation deepens, broad clefts descend to the calcified zone. In endstage osteoarthritis, only sclerotic, eburnated bone remains.

### Changes to bone

New bone formation has been implicated in the pathogenesis of osteoarthritis. In early disease, increased loads to the joint may cause trabecular fracture in the subchondral area leading to stiffening of the subchondral plate, thus magnifying the load to the adjacent matrix. Numerous studies have demonstrated an inverse relationship between osteoporosis and osteoarthritis. Patients with osteoarthritis tend to have higher bone density.

Cartilage supported by denser bone may be subjected to increased stress under loading conditions,
leading to more rapid degeneration. Under normal conditions, the underlying subchondral bone functions to assist in dissipating excess load. With increasing subchondral bone stiffness as disease progresses, this protective capacity declines until the sclerotic bone serves instead to concentrate forces into the articular cartilage.

The bone changes of late osteoarthritis consist of subchondral sclerosis, cyst and osteophyte formation. After loss of articular cartilage, the underlying bone becomes thickened and sclerotic. Hypervascularity is frequently detectable by bone scan. Islands of necrotic bone, new bone and fibrocartilaginous metaplasia are commonly seen. Fibrous defects within the subchondral bone may allow egress of joint fluid which, when trapped and repeatedly loaded, causes hydrostatic pressure leading to local bone erosion and cyst formation. Subchondral cysts may become quite large, extending into the metaphysis. At the bony margins, osteophytes with thickened cortices covered with a hyaline-like cartilage extend from the joint lines. Some have considered osteophytes to be a biological attempt at increasing the articulating surface area in response to increased mechanical forces.

Biochemical alterations in osteoarthritis

The progressive loss of proteoglycans from the cartilage matrix correlates with the severity of the osteoarthritic process. The major proteoglycan of articular cartilage is aggrecan, a large molecule of 1.25 kDa with several globular and extended domains. Aggrecan molecules then bind to a hyaluronate chain to form a large proteoglycan aggregate. Aggregates can contain up to 200 aggrecan molecules.

While proteoglycan production is increased in osteoarthritic cartilage, proteoglycan content is diminished. Chondroitin sulfate content is increased, whereas keratan sulfate content decreases. More ominously, there is a progressive decrease in the proportion of aggregating proteoglycans. With the loss of large proteoglycan aggregates, the biomechanical properties of the cartilage change. See also Proteoglycan

Aggregate loss exposes hydrophilic sites in the remaining proteoglycans. This, combined with disruption of the collagen framework, allows the normally underhydrated matrix to imbibe water. The cartilage softens and swells as its water content increases. The collagen content, which remained relatively constant in early osteoarthritis, begins to fall as production of type II collagen eventually decreases with progressive disease. The stability of the collagen fibril, with a half-life of several years, renders collagen loss a relatively late event in the progression of osteoarthritis. Upregulation of metalloproteinases along with loss of tissue-induced metalloproteinase inhibitors leads to enzymatic collagen degradation.

In late osteoarthritis, the chondrocytes start to proliferate forming disparate clones along deep tissue clefts. These cells churn out products more characteristic of immature or embryonic tissues, including chondroitin-4-sulfate, type III and type X collagen, in an attempt at repair. These changes may be associated with superior migration of the tidemark, osteophyte encroachment and the secondary ossification centres seen in advanced osteoarthritis.

Major Clinical Features and Complications

A long history of slowly progressive pain, stiffness and disability are hallmarks of osteoarthritis. Physical findings include limping, joint enlargement and deformity, joint contractures, and sterile effusions. Characteristic radiographic changes involve (1) loss of normal joint space, (2) subchondral sclerosis, (3) marginal osteophytes, and (4) subchondral cysts.

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For osteoarthritis of the hips and knees, patients generally present with complaints of pain, especially on weight bearing, and progressive joint stiffness. Symptoms may also include a sense of weakness and feelings of instability. Classically, symptoms of pain and stiffness initially improve with activity. Night pain appears later and is suggestive of endstage osteoarthritis and the need for surgical intervention. Candidates for hip osteotomy, a surgical technique to reorient the surface of the joint, may report relief of pain through repositioning of the leg. Patients with arthritis of the hip often complain of groin pain and may present with knee pain. On occasion, knee osteoarthritis masquerades as hip pain, or generalized lower extremity pain. It is important to distinguish pain of intraarticular disease from pain due to extraarticular pathology such as muscle fatigue, bursitis, tendinitis, radiculopathy and vascular claudication. Characterization of the pain by location, time of occurrence, and association with limb position and activity, combined with careful trauma and medical history, assist in separating intraarticular from extraarticular pain.

Clinical evaluation should begin with an observation of stance and gait. Apparent leg lengths and alignment are assessed. Varus (‘bowed leg’) and valgus (‘knock knee’) deformities are readily observed in patients with osteoarthritis of the knees. Range of motion, strength and painful arcs should be documented. Flexion and adduction contractures along with loss of internal rotation are commonly found in patients with osteoarthritis of the hips. Provocative manoeuvres may differentiate pain and impingement from a torn labrum or meniscus from osseous or osteophyte impingement.

Radiography of the affected joints confirms the diagnosis in patients with moderate to severe osteoarthritis and allows for preoperative planning in those who are candidates for surgery. An anteroposterior radiograph of the pelvis followed by anteroposterior and lateral views of the affected hip are commonly obtained to evaluate osteoarthritis of the hip. The degree and location of joint space narrowing - whether medial, superior or global - are readily appreciated on the anteroposterior view. Inferior joint space loss is best seen on a ‘frog’ lateral view. False profile and additional views of the hip may be needed when osteotomy is being considered. Evaluation of knee arthritis commonly includes a standing radiograph of both knees with the beam directed parallel to the affected joint surface followed by anteroposterior, lateral and merchant views of the affected knee. Standing alignment films are useful in planning bone cuts for total knee replacement and osteotomy. Radiographs for patients with advanced osteoarthritis depict complete joint space loss with subchondral sclerosis, exuberant osteophyte formation and multiple subchondral cysts. This is in contrast to rheumatoid arthritis or other inflammatory arthritides where loss of joint space is seen in association with marginal erosions and osteopenia.

Radiographically inapparent osteoarthritis can be diagnosed by bone scan, arthroscopy and magnetic resonance imaging (MRI). While early osteoarthritic changes are readily appreciated on MRI, this investigation has not been used routinely to provide additional information in the treatment or diagnosis of osteoarthritis except when underlying osteonecrosis is suspected. Bone scan will demonstrate increased uptake to the subchondral region of osteoarthritic joint surfaces and is occasionally used to document the presence of osteoarthritis before the appearance of definitive radiographic signs. Cartilage softening, fibrillation, delamination and loss can be most directly assessed arthroscopically. Patients who are potential candidates for cartilage-resurfacing procedures may be identified by arthroscopy and MRI. See also Magnetic Resonance Imaging.

Laboratory studies are obtained infrequently. A complete blood count, sedimentation rate, and rheumatological studies may be obtained in the younger patient to evaluate for inflammatory arthritides.
Joint aspiration with cell count, culture and crystal analysis is important when infection or crystalline arthropathy is suspected. In patients with early or unusual patterns of severe osteoarthritis such as bilateral shoulder involvement, serum iron studies may be obtained to evaluate for haemochromatosis. Rarely, ochronosis detectable by excess homogentisic acid in the urine may produce severe osteoarthritic-like changes in joint cartilage. Assays of synovial fluid and serum for metabolic markers of osteoarthritis are under development but not yet available for disease detection and monitoring.

**Approaches to Management**

Treatment for osteoarthritis has traditionally focused on obtaining symptomatic relief through antiinflammatory agents and analgesics. Preventive measures such as recommendations for weight loss and exercise in the obese patient and activity modification for the middle-aged athlete have been limited. New therapies, both medical and surgical to prevent, delay or reverse the osteoarthritic process are under active clinical investigation. Experimental drugs include a new class of cyclooxygenase-2 selective nonsteroidal antiinflammatory medication, tetracyclines, hyaluronic acid derivatives, and growth factor and cytokine manipulation. New surgical interventions such as autologous chondrocyte implantation, osteochondral grafting, stem cell transplantation and tissue-engineered cartilage healing devices are in various stages of development. Gene therapy to modulate the cellular response to injury and disease is another area of intense research activity. See also Human Gene Therapy

**Preventive measures**

Efforts to prevent osteoarthritis centre around correction of biomechanical abnormalities or joint incongruities resulting from trauma, dysplasia, obesity and activity which are known to contribute to the development of the disease. Antiinflammatory medications may provide symptomatic relief, but do not prevent progression of osteoarthritis in humans.

Patients with osteoarthritis of the weight-bearing joints frequently obtain symptomatic relief with weight loss. Activity modification to reduce impact and loading of affected joints also delays the onset of disabling pain. Patients should avoid prolonged standing or carrying heavy loads. Low-impact aerobic activities such as cycling and water-based exercises assist in weight reduction, muscle strengthening and general fitness. Studies show that improved fitness alone can decrease debilitation from osteoarthritis. Physical therapy may be useful in maintaining muscle strength and range of motion.

Poorly reduced intraarticular fractures can lead to osteoarthritis in the affected joint within a few years. Because a mismatch of only 1 mm in a weight-bearing joint such as the ankle can decrease contact surface area by 42%, thereby markedly increasing load per unit area, anatomical reduction is important. Anatomical reduction by open reduction with internal fixation of intraarticular fractures of the weight-bearing surfaces about the ankle, knee and hips are important treatments in decreasing the incidence and slowing the development of osteoarthritis in these severely injured joints.

**Medical treatments**

Current medications effectively relieve pain and inflammation in patients with mild to moderate osteoarthritis but do not retard or reverse structural and metabolic changes inherent to the disease process. Investigation into the use of various metalloproteinase inhibitors, growth factors and cytokines may yield compounds that prevent or delay the progression of osteoarthritis.

*Antiinflammatory agents*

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Nonsteroidal antiinflammatory drugs (NSAIDs) are superior to placebo in relieving osteoarthritic pain. They have both a central analgesic effect and a peripheral effect in reducing the inflammatory response through prostaglandin inhibition. Long-term NSAID use may therefore adversely impact other prostaglandin-regulated processes, most commonly within the renal and gastrointestinal systems. The risk of adverse effects are increased in elderly and chronically ill patients. In 1991, morbidity from chronic NSAID use was estimated at 76 000 hospitalizations and 7600 deaths annually in the United States. Analgesics such as acetaminophen (paracetamol) are reported to be equally effective as NSAIDs in reducing pain from osteoarthritis. A new class of drugs that act selectively to inhibit cyclooxygenase-2 (COX-2), the enzyme important in prostaglandin synthesis, is under development. Selective COX-2 inhibitors may relieve arthritis pain without significantly affecting cyclooxygenase-1 (COX-1), thereby potentially sparing COX-1-dependent platelets, renal and gastrointestinal systems. Intraarticular corticosteroid injections may be used as a temporizing measure for endstage osteoarthritic joints. Because laboratory studies suggest that corticosteroids may damage healthy articular cartilage, intraarticular steroid injections are not used routinely in the management of early osteoarthritis.

**Intraarticular hyaluronate**

Intraarticular injection of hyaluronic acid (HA) has been approved for clinical use in the treatment of osteoarthritis. HA is a naturally occurring polysaccharide of diverse molecular weight. High molecular weight HA is present in normal synovial fluid where it is thought to confer viscous properties which assist in lubricating and cushioning the joint during motion and loading. To address the observed decrease in HA levels and viscosity found in osteoarthritic joints, the concept of viscosupplementation through injection of HA was proposed. Intraarticular injection appeared to inhibit articular cartilage degeneration in several animal models of osteoarthritis. Clinical studies yielded mixed results. Several studies demonstrated sustained pain relief with improved function following serial injections of HA. When compared with placebo, these effects appeared more pronounced only in older patients with severe osteoarthritis. No significant differences were found between treatment with intraarticular HA and intraarticular corticosteroid in one study, or between HA and placebo in other studies. Adverse effects included acute local inflammatory reactions that were injection related, but not necessarily HA related. The mechanism of action for intraarticular HA is unclear. Analysis of the available literature has not yielded a correlation between molecular weight and efficacy, suggesting that perceived positive effects may be pharmacological or for reasons other than the physical effects of viscosupplementation. Leading unproven theories include possible antiinflammatory properties, local analgesic effects and speculation that injected HA may stimulate the production of chondroprotective substances by synovial cells.

**Dietary supplements**

Several dietary supplements have gained popularity in the lay press for chondroprotective and reparative properties. These agents include chondroitin sulfate, glucosamine sulfate, shark cartilage and others. Glucosamine sulfate administered either orally or by parenteral injection may be effective in relieving arthritic pain and improving function. Limited reports suggest that oral administration of chondroitin sulfate appears to reduce the requirement for NSAIDs or acetaminophen (paracetamol). Several recent reports suggest that chondroitin sulfates may exert an antiinflammatory effect similar to that of a mild NSAID and are better tolerated than standard NSAIDs. There are currently no long-term double-blind placebo-controlled studies demonstrating structural benefits to articular cartilage in humans following ingestion of these compounds.

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New developments

By neutralizing the effects of destructive enzymes such as collagenase, metalloproteinase inhibitors may exert chondroprotective effects. Tetracycline antibiotics such as doxycycline appear effective in decreasing articular cartilage collagenase activity. A multicentre clinical trial evaluating the effects of doxycycline on the progression of knee osteoarthritis in overweight women is being conducted. Other metalloproteinase inhibitors such as glycosaminoglycan polysulfuric acid derived from bovine tracheal cartilage and rumalon, another glycosaminoglycan-peptide complex, are also under clinical investigation.

Manipulation of growth factors and cytokine levels through exogenous administration or gene therapy to modulate the cellular response to injury represent another strategy to prevent or reverse the osteoarthritic process. Transforming growth factor $\beta$ and insulin-like growth factor 1 are under intensive investigation.

Surgical treatment

Patients have traditionally been referred for surgical intervention consisting of total joint replacement only for endstage osteoarthritis. Arthroscopic lavage may provide symptomatic relief for a limited period of time. Increased experience with reconstructive and salvage osteotomies intended to prevent or delay the development of endstage osteoarthritis supports evaluation of patients for surgical treatment options earlier in the disease process. New developments in tissue and cell transplantation offer hope for preventing osteoarthritis through cartilage resurfacing, regeneration and repair.

Total joint replacement

Total joint replacement of the hip and knee offers excellent pain relief and restoration of acceptable joint function with good long-term results and a low rate of major complications in elderly patients. Patient satisfaction is high with demonstrated improvement in quality of remaining life. Good results have also been obtained following unicompartmental knee replacements in appropriately selected patients. Joint replacements in younger patients provide the same level of symptomatic relief, but are associated with higher rates of complications and early failure.

The major cause of failure in total joint arthroplasty is wear debris formation leading to osteolysis and subsequent implant loosening. Most total joint implants are metal to plastic bearings consisting of cobalt chrome metal articulating with ultra-high molecular weight high-density polyethylene (UHMWHDP). With cyclic loading and impact, especially in the younger more active patient, there is wear of the UHMWHDP by mechanisms such as adhesion, abrasion, pitting and delamination. These wear mechanisms produce small polyethylene particles (frequently less than 1 $\mu$m) that are opsonized and phagocytosed by tissue macrophages. These activated macrophages produce proinflammatory molecules, cytokines, eicosanoids and growth factors that stimulate the osteoclast to resorb bone locally and to amplify the osteolytic and inflammatory response. Young osteoarthritic patients with oligoarticular disease are particularly susceptible to this response because they are both more active and immunoreactive than elderly patients. Concern over prosthetic longevity and multiple revisions reduce the utility of total joint arthroplasty in physiologically younger and more active patients. See also Macrophages

Osteotomy

Osteotomies about the knee and hip in the adult may prevent or delay the onset of osteoarthritis by
improving the biomechanics of the joint in the treatment of residual dysplasia, malalignment and osteonecrosis. The principle of osteotomy is to correct the malalignment that is overloading and damaging the articular surface. By redirection, the excess load is shifted to the more normal joint surface. Reconstructive osteotomies are performed to correct the deformity before the development of clinically apparent osteoarthritis. When osteoarthritis is present, salvage osteotomies may be performed with the goal of improving function and delaying the arrival of endstage osteoarthritis.

Articular cartilage transplantation and regeneration

Large chondral defects in load-bearing joints generally heal incompletely with a mechanically inferior fibrocartilage. Lesions greater than 1 cm frequently fail to exhibit any significant healing response, leading to persistent pain and disability. If left untreated, osteoarthritis develops in these joints. Cartilage resurfacing and regeneration are the two main surgical strategies to prevent or delay the onset of osteoarthritis in this setting.

Fresh osteochondral shell allograft transplants have been used with success in resurfacing large isolated lesions to the femoral condyles and to the patella or trochlea. Clinical studies into constructing mosaic surfaces using autologous osteochondral plugs represent another resurfacing concept. Extensive research into tissue-engineered cartilage transplants may yield cartilage grafts that eventually prove to slow or prevent the development of osteoarthritis following osteochondral injuries.

Efforts to stimulate repair and regeneration of the articular surface include microfracture, abrasion arthroplasty, subchondral drilling and the transplantation of chondrogenic cells and tissues. Abrasion arthroplasty, subchondral drilling and microfracture are variations of the technique to disrupt the subchondral bone in order to induce fibrin clot formation and the migration of reparative stem cells from the bone marrow to the cartilage defect. These techniques appear to result in a fibrocartilaginous repair tissue with unpredictable long-term results. Chondrocyte, periosteal and perichondrial tissue and cell transplantation represent attempts to introduce exogenous repair cells to the defect. Autologous chondrocyte implantation (ACI) using cultured chondrocytes injected under a periosteal flap has demonstrated early clinical success in the treatment of full-thickness articular cartilage defects. To date, ACI has been shown to repair chondral defects with hyaline-like material but not to heal osteoarthritic defects with articular cartilage. The long-term efficacy of ACI is still under investigation.

Summary

Osteoarthritis is a major public health issue for an ageing population. It is a chronic, progressive disease of unknown aetiology which causes significant pain and disability. Preventive measures are currently inadequate, with treatment options centred around relief of pain and restoration of acceptable function through replacement of severely affected joints with metal and plastic prosthetic implants.

Progress towards elucidating the pathophysiology of the disease has led to research into diverse strategies for preventing, delaying and reversing osteoarthritis. The plethora of approaches is testimony to the many pathways by which healthy joints become osteoarthritic. The osteoarthritic process probably involves a finely tuned system of checks and balances with limited tolerance for the disruption of any component.

Individualized gene therapy to address specific imbalances along this pathway, coupled with surgical correction of joint trauma and dysplasia, may eventually eradicate the disease. Efforts to regenerate and repair articular cartilage through tissue and cell transplantation are complemented by research into...
chondroprotective and chondroregenerative medications. In the near future, combination drug therapy in concert with operative correction of mechanical imbalances and chondral defects may lead to disease modification through multidisciplinary collaboration. The potential role of maintaining normal body weight and musculoskeletal fitness in preventing the onset of debilitating osteoarthritis cannot be overemphasized.

**Further Reading**


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**Glossary**

**Abrasion arthroplasty**
A surgical procedure in which damaged articular cartilage is removed and the underlying subchondral bone is abraded using motorized instruments until a bleeding surface is exposed. It is theorized that repair cells from the bone marrow will then reconstitute the articular surface. This does not consistently occur. When it does happen, the repair tissue is frequently a fibrocartilage with inferior mechanical properties.

**Chondroprotective agent**
A substance that reduces or eliminates abnormal cartilage cell metabolism or the breakdown of articular cartilage.

**Chondrolysis**
Disruption of the structural integrity of articular cartilage, frequently by enzymatic degradation.

**Collagenase**
An enzyme that disrupts collagen, a major structural protein found in articular cartilage.

**Cyclooxygenase**
An enzyme complex that converts certain fatty acids into prostaglandins and other active molecules. This enzyme is inhibited by drugs such as aspirin. Inhibition of prostaglandin synthesis is thought to account for the antiinflammatory effects of aspirin and nonsteroidal antiinflammatory medications.

**Cytokine**
Cytokines are a unique family of growth factors. Secreted primarily from leucocytes, cytokines stimulate both the humoral and cellular immune responses, as well as the activation of phagocytic cells.

**Dysplasia**
When used to describe joints, this term refers to abnormal shape of one or both of the articulating surfaces. Joint dysplasia is frequently developmental in nature.
**Eicosanoids**
A family of fatty acids that are metabolized into prostaglandins and other substances. Aspirin and nonsteroidal antiinflammatory medications affect this process.

**Fibrocartilage**
This subtype of cartilage is composed primarily of Type I collagen. It is the normal type of cartilage found in tendons and ligaments. Normal articular cartilage contains very little Type I collagen. When attempts to regenerate articular cartilage leads to a repair tissue with mostly Type I collagen, this tissue is referred to as 'scar cartilage'.

**Growth factors**
Growth factors are proteins that bind to receptors on the cell surface, with the primary result of activating cellular proliferation and/or differentiation.

**Hyaline cartilage**
This subtype is composed primarily of Type II collagen. Articular cartilage is one of the tissues with a collagen content that is predominantly Type II collagen and is therefore a hyaline cartilage. Hyaline cartilages and repair tissues which lack the functional architecture of articular cartilage cannot be considered equivalent to articular cartilage.

**Hyaluronic acid**
A polymer composed of repeating units of specific sugars which may be of extremely high molecular weight, up to several million daltons. This polymer forms the core of complex proteoglycan aggregates within the extracellular matrix of articular cartilage.

**Macrophages**
Macrophages are derived from blood monocytes. They play important roles in the immune system ranging from the killing of bacteria and tumour cells to stimulation of other immune cells to antigen presentation. Macrophages become stimulated after ingestion of foreign materials such as metal and plastic debris from joint prostheses. They are thought to play a key role in periprosthetic osteolysis.

**Mesenchymal cells**
Pluripotent cells originating from the mesoderm which gives rise to the connective tissues and to the blood cells.

**Metalloproteinase**
This class of enzyme describes peptide hydrolases which use a metal in a catalytic mechanism. This group of enzymes includes the collagenses. Overactivity of these enzymes are thought to play a role in the arthritic process.

**Microfracture**
A surgical procedure in which potential repair cells from blood and bone marrow gain access to an articular cartilage defect through penetration of the subchondral bone using a sharp awl.

**Osteochondral defect**
An injury or defect to articular cartilage that extends through the full thickness of the cartilage to involve the underlying bone.

**Osteolysis**
In a discussion of total joint replacements, osteolysis refers to the dissolution of bone surrounding an
implant that is believed to be caused by the ingestion of particulate debris by macrophages. Bone loss can also occur when normal weightbearing stresses are changed by the position or shape of a metal prosthesis.

**Osteonecrosis**
A joint surface can collapse when the supporting bone dies. Osteonecrosis refers to the death of bone resulting from poor blood supply to a region of bone. Frequently, the cause of this situation is unknown.

**Osteophytes**
This term refers to bone spurs. When bone spurs surround a joint surface, they serve to expand the surface area available for weightbearing. This phenomenon may be a mechanism by which the body attempts to redistribute abnormally high forces across a particular joint.

**Osteotomy**
In joint reconstruction, bone cuts can be made in specific angular, curved or linear patterns to allow for redirection of an articular surface.

**Patellofemoral joint**
The portion of the knee joint describing the articulation between the patella (or kneecap) and the front of the femur. This joint is also known as the patellofemoral compartment, one of three compartments of the knee.

**Perichondrium**
A thin layer of tissue overlying nonarticular cartilages. This tissue is most commonly obtained from the cartilaginous portion of the ribs. It has been used with limited success in resurfacing defects of articular cartilage.

**Periosteum**
A fibrous tissue covering bone. When used to resurface damaged articular cartilage of the knees with or without the addition of cartilage cells, this tissue is frequently obtained from proximal tibia or distal femur.

**Prostaglandin**
A group of components derived from unsaturated 20 carbon fatty acids via the cyclooxygenase pathway which are extremely potent mediators of a diverse group of physiological processes. Prostaglandins have a variety of important roles in regulating cellular activities, especially in the inflammatory response where they act as vasodilators in the vascular system, cause vasoconstriction or vasodilatation together with bronchodilatation in the lung and act as hyperalgesics.

**Proteoglycan**
A molecule with a protein backbone and sugar residues which is a major component of the extracellular matrix in articular cartilage.

**Subchondral bone**
The bone immediately below articular cartilage. The biomechanical characteristics of this portion of bone are thought to play a major role in the development of osteoarthritis.

**Tibiofemoral joint**
The portion of the knee joint describing the articulation between the femur and the tibia. This joint is subdivided into medial and lateral compartments.
Trabecular bone
Adult bone consisting of mineralized regularly ordered parallel collagen fibres more loosely organized than the lamellar bone of the shaft of adult long bones. This bone is also known as cancellous bone.

Unicompartmental replacement
Resurfacing of the damaged bone and cartilage in only one of the three compartments of the knee.

Viscosupplementation
Using compounds to return more normal viscosity, a physical property of fluids determining the internal resistance of shear forces, to synovial fluid.