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# Pain in Osteoarthritis: Emerging Techniques and Technologies for Its Treatment

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## 1. Introduction

Osteoarthritis (OA) is described as a condition characterised by use-related joint pain experienced on most days in any given month, for which no other cause is apparent. OA is the commonest disease affecting synovial joints and affects more than 40% of the population over 65 years. It affects primarily the knee joints however hip, ankle, shoulder and small joints of hand and feet may be involved.

Previously, OA was considered a wear and tear, degenerative disease that must be accepted as an inevitable consequence of trauma and ageing. With advances in research and understanding of the mechanism of OA progression it is now known as a disease of the synovial joint affecting subchondral bone, synovium, meniscus, ligaments and supporting structures around the joints, including the cartilage.

The pathological changes seen in OA are characterised by focal areas of loss of articular cartilage within the synovial joints, associated with hypertrophy of the bone (osteophytes and subchondral sclerosis) and thickening of the capsule. OA is a chronic, degenerative disease associated with joint pain and loss of function. The primary problem in OA is the damage to the articular cartilage, which triggers a series of other events that culminate in pain and loss/limitation of function in the affected joint.

Undoubtedly, pain, which is the most prominent and disabling presentation of OA, is an increasingly important public health problem especially within an increasing aging population.

## 2. Epidemiology

OA occurs worldwide with higher prevalence in developed societies. It is twice as common in women as in men with a significant familial tendency.

The prevalence of OA increases with age in a progressive manner with 80% radiographic changes in people by the age of 65 years. However only about 25-30% are symptomatic. Primary OA is uncommon before the age of 50 years.

World Health Organisation reports that knee OA is ranked fourth most important global cause of disability in women and the eighth most important in men. Annual arthroplasty rate in over the age of 65 in Europeans vary from country to country but are of the order of

0.5–0.7 per 1000. The annual costs attributable to knee OA are immense. There is therefore a burden on health from both morbidity and cost.

OA is a complex disorder with multiple risk factors.

### 2.1 Risk factors for OA

1. Age > 50 years
2. Crystals in joint fluid or cartilage
3. High bone mineral density
4. History of immobilisation
5. Injury to the joint
6. Joint hypermobility or instability
7. Obesity (weight-bearing joints)
8. Peripheral neuropathy
9. Prolonged occupational or sports stress

### 3 Anatomy of a joint

A brief review of the basic anatomy of a typical synovial joint is presented here to help understand the mechanisms involved in OA-induced damages of the involved joint that culminate in pain and other symptoms of OA.

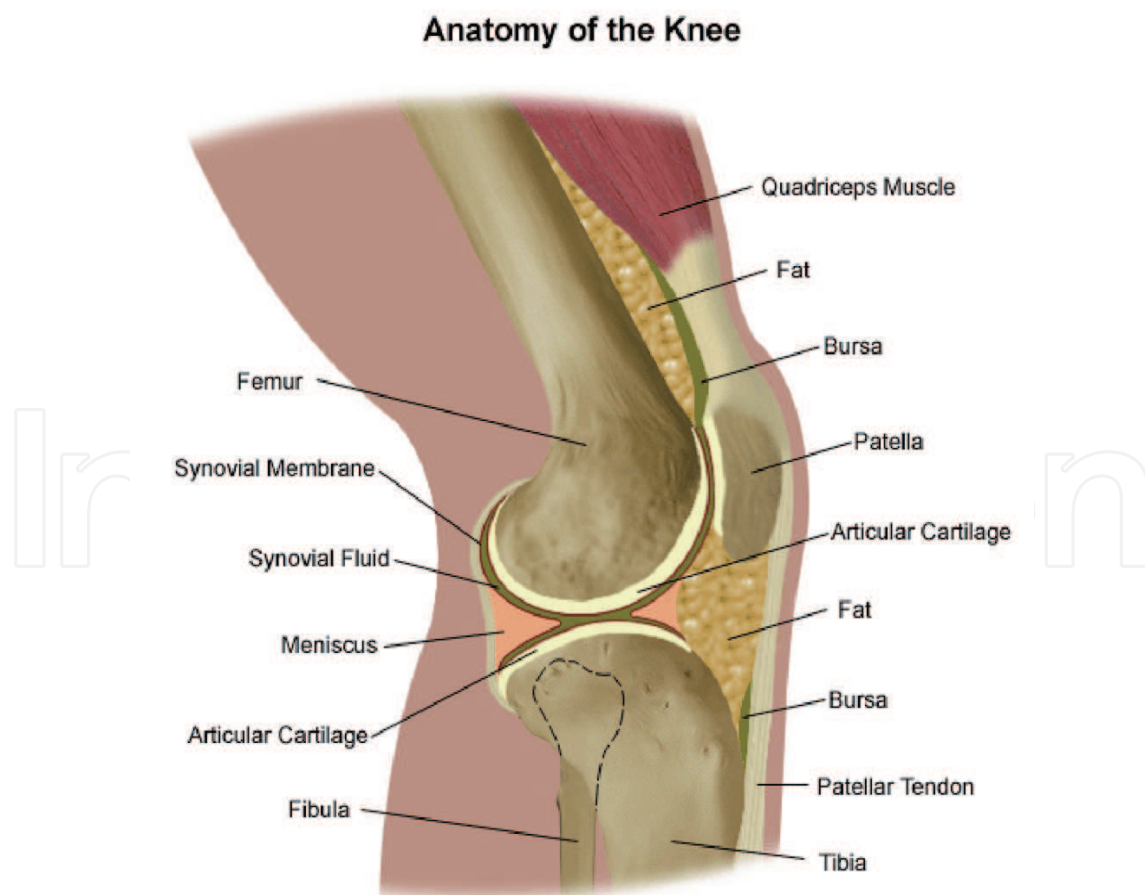


Fig. 1. A typical synovial joint

A joint is where two bones meet. Articular cartilage covers the bone ends which are lubricated by synovial fluid. Seventy to eighty per cent of the cartilage is made up of water and a type II collagen with proteoglycans and glycosaminoglycans produced by chondrocytes. The collagen fibres in the cartilage offer tensile strength to the cartilage because of its architectural makeup. The cartilage, however, contains no intrinsic blood vessels. It receives its nutrition from the synovial fluid. The synovial fluid, which is secreted by the synovial membrane lining the inner surface of the joint, facilitates not only movement but also provides nutrients, phagocytosis and other immunologic functions within the joint. The integrity of a joint is therefore dependent upon its architecture, the cartilage, bone and the supporting structures enclosing the joint. OA in simple terms is a result of alterations in the aforementioned architectural structures within the joint with resultant pain, loss of function and instability in the involved joint. Figure 1 shows the diagram of a typical synovial joint.

#### 4. Sources of nociception in a joint

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. Pain, as generally acknowledged, is mainly a signal that the body has been injured.

The term “nociception” was coined by the Nobel Laureate Sherrington to designate a physiological sensory phenomenon. “Nociception” is derived from “nocere”, the Latin word for “to hurt”. Nociceptors are peripheral sensory organs that are activated when nociceptive stimuli cause tissue damage. These nociceptors are unspecialised, naked nerve endings found close to small blood vessels and mast cells. The functional nociceptive unit is therefore made up of the structural triad of capillary, nociceptor and mast cell. This is the unit that is sensitive to tissue damage. There are also a rich supply of myelinated and unmyelinated fibres innervating the joint capsule, ligaments subchondral bone, periosteum and menisci.

In the anatomy of the joint described above, the cartilage does not contain blood vessels but derives its nutrients from the synovium. The subchondral bone, periosteum, synovium, ligaments, and the joint capsule contain nerve endings that could be the source of nociceptive stimuli in OA. Irritation of the periosteum as a result of remodelling, denuded bone, compression of soft tissue by osteophytes, microfractures of the subchondral bone, effusion and spasm of surrounding muscles has been shown to contribute to the pain that may be felt by patients with OA. So in effect the bone in the periosteum and bone marrow is richly innervated with nociceptive fibres and represents a potential source of nociceptive pain in patients with OA.

#### 5. Pathology and pathogenesis

OA is a heterogenous spectrum of clinical condition affecting mostly joints. No one mechanism explains the various processes seen in the joint of OA. Factors including inflammation, genetic, injury or trauma and joint mechanics have all been implicated in the pathophysiology of OA. Each joint response is a balance of the anabolic and catabolic factors acting in combination with both the extrinsic and intrinsic factors.

Summary of the mechanisms suggested for the pathogenesis of OA are:

- *Matrix loss*: Metalloproteinases (MMPs) such as stromelysin and collagenase which are secreted by the chondrocytes catalyses the degradation of both collagen and proteoglycans resulting in matrix loss

- *Role of inflammatory mediators:* Mediators such as TNF- $\alpha$  and IL-1 stimulate MMPs secretion and this inhibit collagen production.
- *Tissue inhibitors of MMPs:* Tissue inhibitors of MMPs regulate the MMPs. Therefore any disturbance of this regulatory mechanism may lead to increased cartilage degradation and may contribute to the development of OA.
- *Growth factors deficiency:* Growth factors such as insulin-like growth factor and transforming growth factor enhance collagen synthesis and so when these factors are deficient matrix repair is impaired.
- Genetic susceptibility

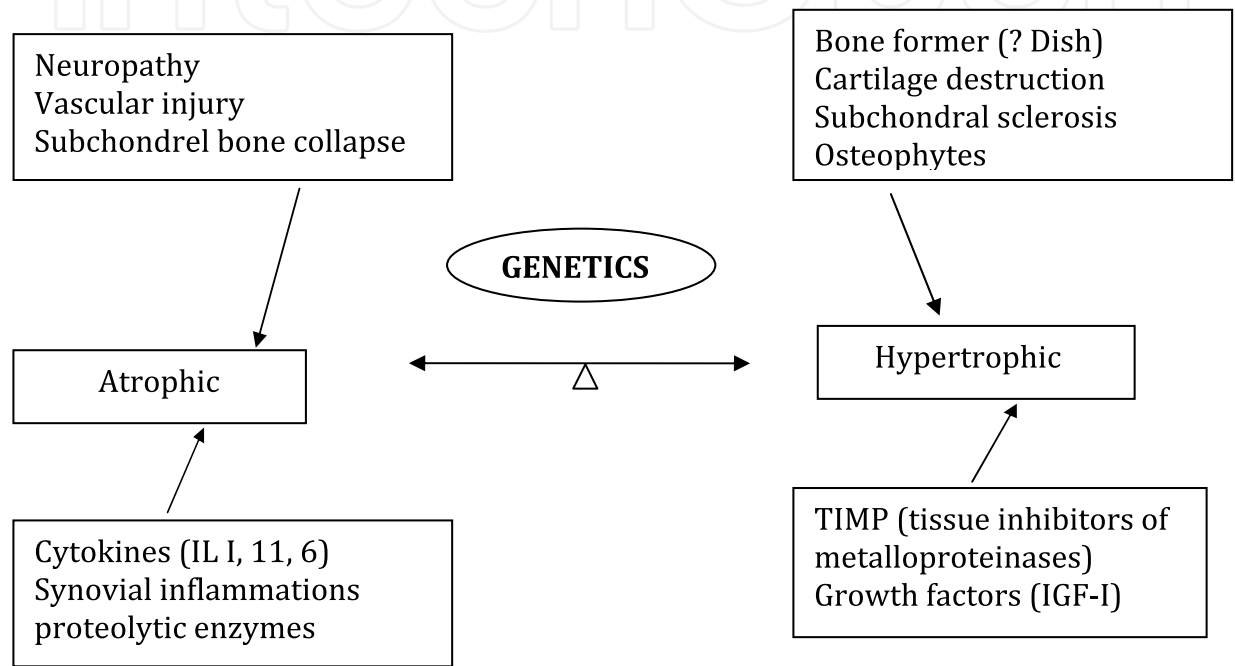


Fig. 2. Different factors that influence OA process.

Stage I	There is proteolytic breakdown of cartilage matrix
Stage II	There is fibrillation and erosion of cartilage surface, accompanied by the release of breakdown products into the synovial fluid
Stage III	Synovial inflammation begins when synovial cells ingest a breakdown product through phagocytosis and produce proteases and proinflammatory cytokines

Table 1. Stages of OA (Martel-Pelletier, 2004)

5.1 Classification of OA

Primary OA	Has no known cause. Common. Related to aging and hereditary. May be localised or generalised. Commonly affects the distal interphalangeal joints of the hands, hip and the knee. The cervical and lumbar spine may be affected.
Secondary OA	Causes include articular injury, obesity, Paget’s disease, or inflammatory arthritis and aging process. May be localised or generalised. May affect any joint and can occur at any age.

5.2 Clinical features

Pain and functional restriction are the main symptoms in OA. The pain is characteristically made worse by movement and relieved by rest.

Signs	Symptoms
Joint tenderness	Joint pain
Crepitus on movement	Joint gelling (stiffening and pain after mobility)
Limitation of range of movement	Joint instability
Joint instability	Loss of function
Joint effusion and variable levels of inflammation	
Bone swelling	
Wasting of muscles	

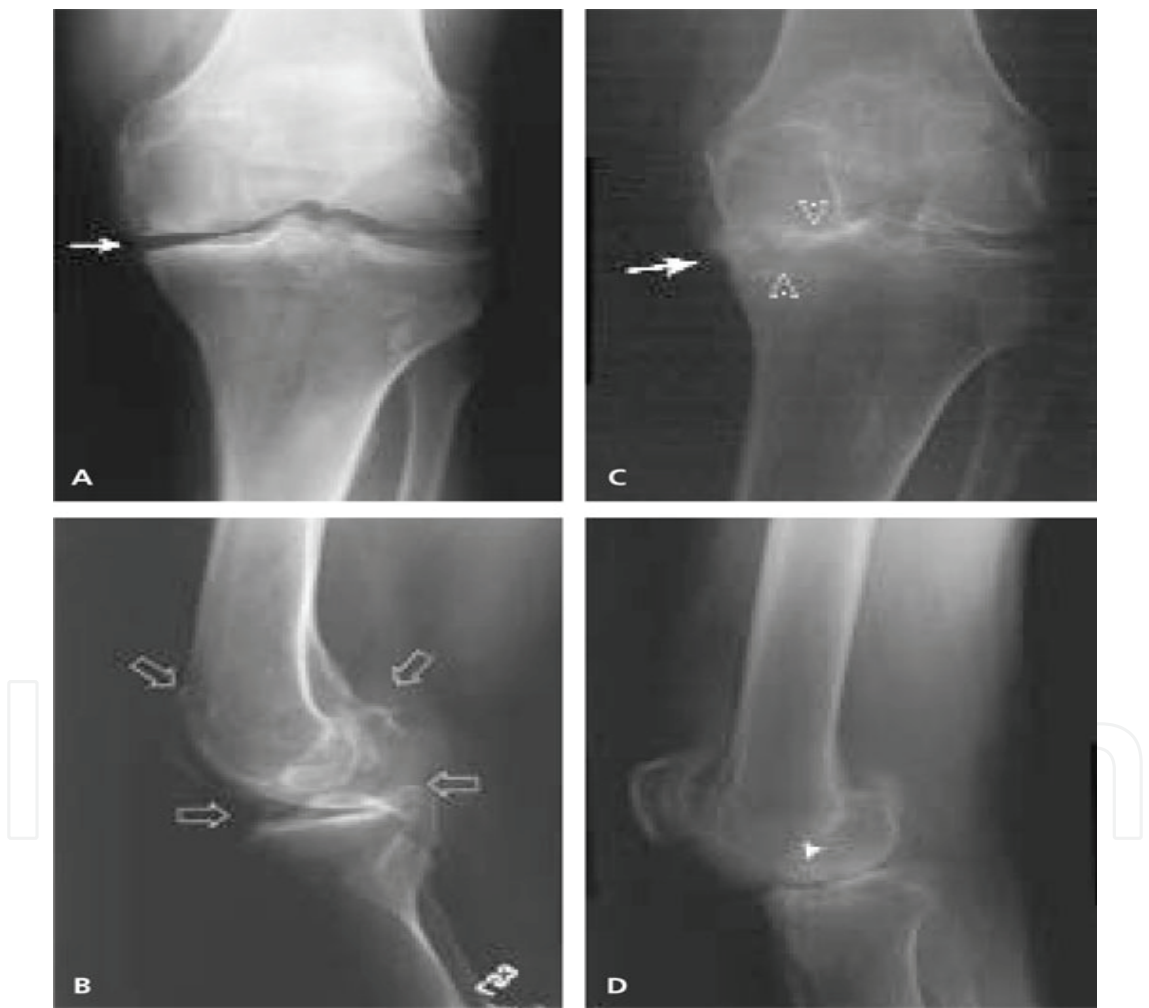


Fig. 3. Radiological changes in Osteoarthritis of the knees. (A) AP view of the left knee shows medial joint space narrowing (arrow). (B) Lateral view shows sclerosis with marked osteophyte formation (arrows). (C) Medial joint space narrowing (white arrow) causing a varus deformity of the knee and collapse of the joint space with destruction of the medial cartilage and the subchondral cortex (open arrow heads). (D) Subchondral cysts are noted (solid arrow head).



### 5.3 Radiological changes in OA

- Joint space narrowing
- Osteophytes
- Bony cysts
- Subchondral sclerosis

### 5.4 Mechanism of pain in OA

#### Summary of process of pain perception

- A noxious stimulus causes stimulation of nociceptors (pain receptors) in the receptor organ (e.g. joint).
- This firing of primary afferent fibres at the site of tissue injury causes axonal release of substance P (SP). This stimulation leads to activation of cells in the dorsal horn of the spinal cord and transmission of the nerve impulse to the midbrain and cortex. Thus, impulses travelling along first order neuron synapse on second-order neuron in the dorsal horn of the spinal cord. The axon crosses to the contralateral side and ascends to synapse on the third-order neurons. The third-order neurons send fibres to the cerebral cortex where conscious perception of the sensation occurs.
- Transmission of sensory information is modulated (inhibited or potentiated) throughout the nervous system by neurons from the midbrain and spinal cord that release endogenous opioids, catecholamines and other neurotransmitters.
- Peripheral nociceptor sensitisation, which is the transmission of impulses at subnormal threshold, occurs following the release of chemical mediators such as prostaglandins and leukotrienes at the site of injury or damage. Continued stimulation by peripheral nociceptors then leads to sensitisation of neurons in the spinal cord. This is known as central sensitisation.

Tissue injury results in the release of inflammatory mediators such as serotonin, bradykinin, calcitonin gene-related peptide (CGRP) and SP, which lead to nociceptor nerve fibre sensitisation in peripheral tissue. These damaged fibres release inflammatory agents causing a spread of increased sensitivity around the area of tissue damage. This is called primary hyperalgesia. The repeated depolarisation of primary afferent fibres leads to a continuous release of neurotransmitters onto the secondary neurons in the spinal cord, resulting in central sensitisation and secondary hyperalgesia. Peripheral pain sensitisation is a feature of osteoarthritis in the joint.

In addition to peripheral pain sensitisation pain in OA, could also be due to local and central sensitisation of pain, pathways resulting in normal stimuli becoming painful with inflammation being an important feature in the process of OA.

Most of the substances involved in inflammation such as proinflammatory cytokines and bradykinins interact with the nociceptive fibres present within the joint and induce hyperalgesia and allodynia seen in patients with chronic inflammatory joint disease like OA. These mechanisms acting in concert could participate in the progression of hyperalgesia to chronicity.

### 5.5 Progression of OA to chronicity

Chronic pain (CP) is pain that persists for a month beyond the usual course of an acute disease or a reasonable time period for an injury to heal.

CP differs from the acute process not only in the duration of its course but also the different receptors involved in the mechanisms of action for acute pain and CP.

Those most involved in the acute process are  $\alpha$ -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptors, while those of primary importance in the sensation of CP are N-methyl-D-aspartate (NMDA) receptors. Activation of NMDA receptors causes the release of peptide neurotransmitter SP, which amplifies the pain by causing the spinal neurons carrying the pain to be easily stimulated.

Elevated levels of SP in spinal fluids have been documented in patients with OA and fibromyalgia. The progression of nociception from an acute to a chronic process has yet to be fully understood. However, recent evidence from animal experiments as well as human research suggests that peripheral mechanisms in acute pain and long-term potentiation (LTP) of neuronal sensitivity to nociceptive inputs in the dorsal horn of the spinal cord may underline the transition from acute to a chronic process.

LTP in spinal nociceptive systems has been suggested as one of the mechanisms underpinning the transition of acute pain to CP. It seems possible that LTP may underlie some forms of afferent induced hyperalgesia and that simultaneous activation of NMDA; SP neurokinin-I (NK-I) and glutamate receptors are required for the induction of spinal LTP. Therefore, it is likely that the conditioning stimuli that induce synaptic LTP in the superficial spinal dorsal horn are similar to those that trigger hyperalgesia. LTP is likely to occur in both the sensory and the affective pain pathways. Additionally, spinal LTP and injury-induced hyperalgesia share signal transduction pathways, which make use-dependent LTP an attractive model of injury-induced central sensitisation and hyperalgesia.

#### Summary of progression to chronic pain state

1. Rapid, intense stimulation of CA1 neurons in the hippocampus depolarizes them.
2. Binding of Glu and D-serine to their NMDA receptors opens them.
3.  $\text{Ca}^{2+}$  ions flow into the cell through the NMDA receptors and bind to calmodulin.
4. This activates calcium-calmodulin-dependent kinase II (CaMKII).
  - CaMKII phosphorylates AMPA receptors making them more permeable to the inflow of  $\text{Na}^+$  ions and thus increasing the sensitivity of the cell to depolarization.
  - In time CaMKII also increases the number of AMPA receptors at the synapse.
5. Increased gene expression (i.e., protein synthesis – perhaps of AMPA receptors) also occurs during the development of LTP.
6. Enlargement of the synaptic connections and perhaps the formation of additional synapses occur during the formation of LTP.

## 6. Treatment: emerging techniques and technologies

The modes of treatment for OA have always focus on decreasing pain and improving function ranging from information, education, physical therapy and aids, through analgesics, non-steroidal anti-inflammatory drugs and joint injections, and to surgery in which all or part of the joint is replaced with plastic, metal or ceramic implants.

OA is complex in genetics, pathogenesis, monitoring and treatment however, the principal goals of management are:

- Education of the patient about OA
- Pain relief
- Achieving and maintaining optimal joint and limb function
- Reducing adverse factors to beneficially modify the OA process and its outcome.



Despite huge laboratory and clinical research, there are no proven diseases modifying therapies for OA. However, emerging orthopaedic surgical procedures may help to alleviate the attendant pain and functional loss resulting from joint damage in OA.

Some of the surgical approaches in the management of OA include

- Arthroscopic approach
- Osteotomies
- Total joint replacements and arthrodesis
- Tissue engineering and biologic therapies
  - Autologous Chondrocyte Implantation (ACI)
  - Meniscal Transplantation (MT)

### 6.1 Arthroscopic procedures for OA

Arthroscopic surgery is a routine surgical procedure for joint debridement and lavage in the management of OA since the 1980s. The advent of this technique has permitted less invasive access to joints and the opportunity to intervene earlier in the course of joint destruction, potentially to delay and/or prevent a predictably progressive degenerative pathway. However, in recent times the only indication where this technique is thought to be of benefit is in the management of OA with a superimposed structural lesion such as a meniscal tear in which arthroscopic partial meniscectomy (APM) is performed simultaneously.

There is a strong research and clinical evidence that patients with symptoms attributable to knee OA per se, and not meniscal tear, do not improve following arthroscopic lavage and debridement. Whether APM is useful in patients with symptomatic meniscal tear and concomitant OA is unclear at this stage. This is an area of investigation at the moment.

### 6.2 Osteotomies

Osteotomies are performed to restore a more anatomic biomechanical environment and prevent or delay the onset of OA or slow its progression.

In symptomatic patients with OA, osteotomy is performed to realign joints with the aims of relieving pain and delaying the onset or progression of OA. Osteotomy and joint preserving surgical procedures should be considered in young adults with symptomatic OA, especially in the presence of dysplasia or varus/valgus deformity.

#### 6.2.1 Indications

- As an adjunct in younger patients with predominantly unicompartmental OA
- Age less than 60 years
- 10 to 15 degrees of varus deformity on weight bearing radiographs
- Preoperative motion arc of at least 90 degrees
- Flexion contracture less than 15 degrees
- Ability and motivation to effectively and safely perform rehabilitation

#### 6.2.2 Contraindications to osteotomy

- Lateral compartment loss of joint space
- Lateral tibial subluxation greater than 1 centimeter
- Medial bone loss greater than 2 to 3 millimeters
- Ligamentous instability
- Inflammatory arthritis

6.2.3 Surgical types and methods

<i>Surgical Types</i>	<i>Methods</i>
<b>Medial compartment knee OA and varus deformity</b> <ul style="list-style-type: none"><li>• Advantages</li></ul>	High tibial osteotomy is performed either by removing a wedge of bone from the lateral proximal tibia or more commonly by opening wedge space in the a medial proximal tibia. Permits the knee to adapt a more valgus alignment. Transfers load from the damaged medial compartment to the more normal cartilage of the lateral compartment.
<b>Lateral compartment knee OA and varus deformity</b> <ul style="list-style-type: none"><li>• Advantage</li></ul>	This is a distal femoral osteotomy in which a wedge of bone is removed from the medial distal femur or a wedge is opened in the lateral aspect. Shifts the load to the healthier medial compartment.



Fig. 4. AP radiograph of medial opening wedge high tibial osteotomy performed for medial compartment osteoarthritis.

### 6.3 Total joint replacements and arthrodesis

Total joint replacement (TJR) has to be considered in patients with radiographic evidence of hip/ knee OA who have refractory pain and disability. Principally, OA occurs less commonly at ankle, elbow, and wrist and thus total joint replacements are less frequent at these sites than at the hip or knee. In the last few years, interest in total knee arthroplasty has resulted in a proliferation of prosthetic designs, and many different types are now available.

The indications for TJR have evolved and are expanding. Currently TJR are offered to patients earlier in the course of the disease as the risks of complications associated with TJR have reduced dramatically.

The prostheses available are:

1. *Condylar replacements*: The joint surfaces alone are replaced. Ligaments then are needed to provide stability.
2. *Hinge-type prostheses*: In this type the ligaments are sacrificed and stability is provided by the design of the prosthesis itself.

The selection of a suitable prosthesis is dependent on the type and the indications

Types of prostheses

1. Unicondylar

This is an anatomically designed replacement for either the medial or the lateral femoral tibial articulation. It is designed to allow 120 degrees of flexion. The *unicondylar* prosthesis is used only for compartmental OA.

2. Duocondylar

The femoral component of the duocondylar prosthesis is similar in shape to that of the unicondylar model except that there is no anterior flange and instead the halves are connected by an anterior cross bar which is countersunk during insertion. Because of its anatomical shape, it is most suitable when deformity, instability, and flexion contracture are not too severe.

3. Geometric

The prosthesis is non-anatomical in that the curvature of the femoral component is of constant radius. The plastic tibial component is in one piece, with two halves connected by an anterior bar. The prosthesis is designed to allow a 90-degree arc of motion. The cruciate ligaments are preserved. Two sizes are available.

4. Guepar

The Guepar is a Vitallium hinge prosthesis (improved over the Young model) which is fully constrained, providing motion in a fixed axis without rotation. Guepar prosthesis was used in knees with extreme deformity or instability due to rheumatoid arthritis and OA.

Innovation continues to characterize the TJR field. This clinical dilemma has stimulated a search for biomaterials that produce less wear debris and, in turn, cause less osteolysis, attendant bone loss, and implant failure. This is the rationale for several developments, including highly cross-linked polyethylene and ceramic-on-ceramic and metal-on-metal bearing surfaces.

### 6.4 Surgical and biologic procedures

Advances in tissue engineering and biologic therapy have led to a few limited successes. Perhaps the most notable is autologous chondrocyte implantation (ACI).

Indications

1. Age <50 years
2. Isolated cartilage defects typically greater than 3 cm<sup>2</sup> in size

This procedure attempts to repair a symptomatic cartilage defect (Figure 3A) through implantation of chondrocytes grown *ex vivo* from a small cartilage biopsy sample obtained from the patient in a staging arthroscopy. After debridement of any degenerated tissue in the defect, a patch material, either periosteum from the patient or a synthetic collagen membrane, is sutured over the defect to create a watertight chamber into which the chondrocyte suspension is injected (Figure 3B). The chondrocytes attach to the subchondral bone and produce cartilage matrix, eventually filling the defect with hyaline-like cartilage.

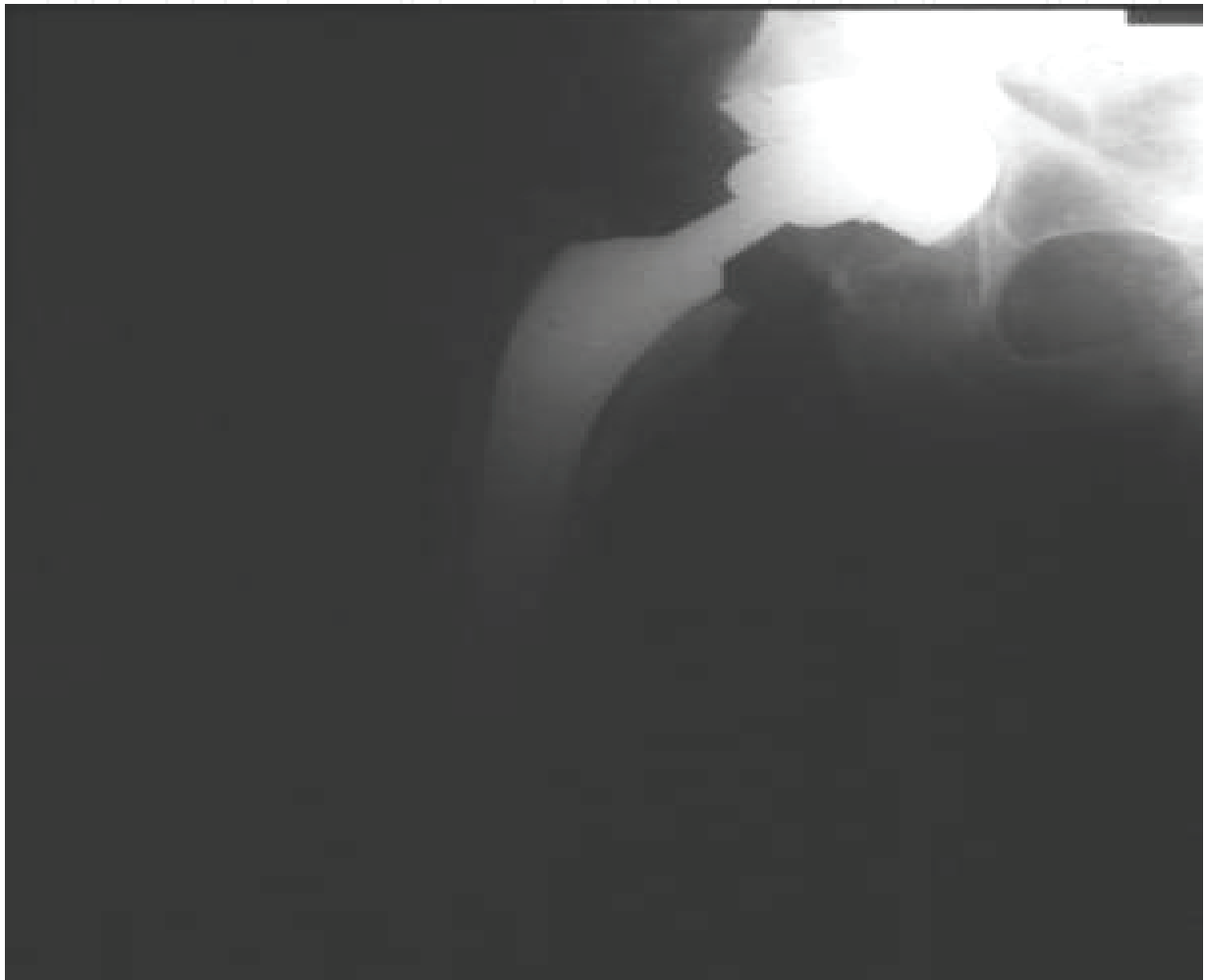


Fig. 5. Total hip replacement

### 6.5 Conclusion

It is clear from the foregoing that any simple unitary concept about the link between joint damage and symptoms in OA 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.

In the absence of effective disease-modifying therapy, many patients with OA progress to advanced joint destruction. Therefore, surgery plays an important role in the management of OA. Advances in biomaterials and tissue engineering will continue to create exciting new opportunities to integrate surgical approaches in OA care.



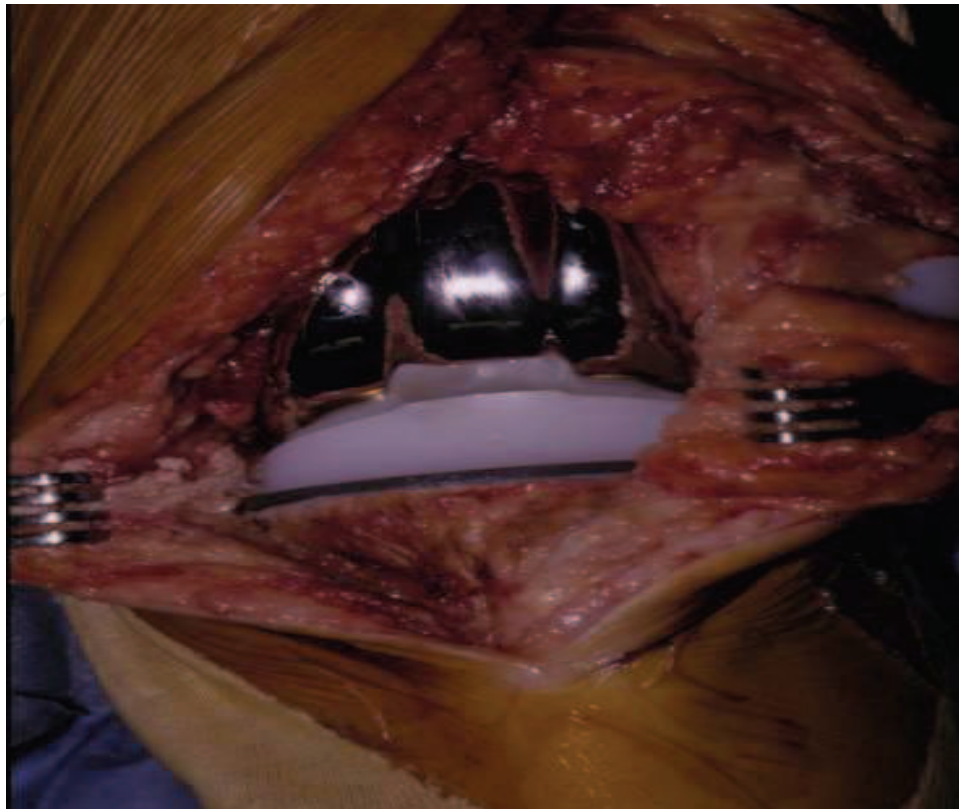
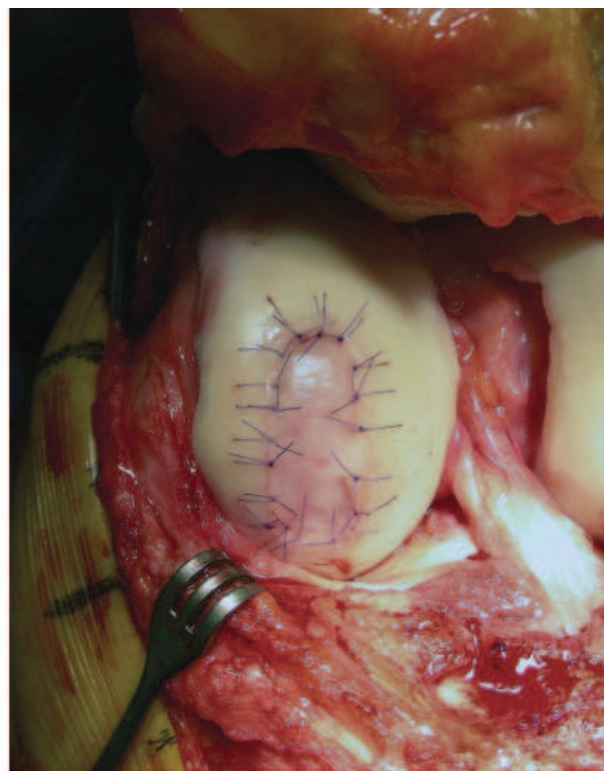


Fig. 6. Total knee replacement



**A**



**B**

Fig. 7. **A**, Cartilage defect on femoral condyle.  
**B**, Cartilage defect treated with autologous cartilage implantation

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## **Biomedical Science, Engineering and Technology**

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This innovative book integrates the disciplines of biomedical science, biomedical engineering, biotechnology, physiological engineering, and hospital management technology. Herein, Biomedical science covers topics on disease pathways, models and treatment mechanisms, and the roles of red palm oil and phytochemical plants in reducing HIV and diabetes complications by enhancing antioxidant activity. Biomedical engineering covers topics of biomaterials (biodegradable polymers and magnetic nanomaterials), coronary stents, contact lenses, modelling of flows through tubes of varying cross-section, heart rate variability analysis of diabetic neuropathy, and EEG analysis in brain function assessment. Biotechnology covers the topics of hydrophobic interaction chromatography, protein scaffolds engineering, liposomes for construction of vaccines, induced pluripotent stem cells to fix genetic diseases by regenerative approaches, polymeric drug conjugates for improving the efficacy of anticancer drugs, and genetic modification of animals for agricultural use. Physiological engineering deals with mathematical modelling of physiological (cardiac, lung ventilation, glucose regulation) systems and formulation of indices for medical assessment (such as cardiac contractility, lung disease status, and diabetes risk). Finally, Hospital management science and technology involves the application of both biomedical engineering and industrial engineering for cost-effective operation of a hospital.

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