INTRODUCTION
1. Introduction

Autoimmunity is the failure of an organism in recognizing its own constituent parts as self, which allows an immune response against its own cells and tissues.\textsuperscript{1-2} Any disease that results from such an aberrant immune response is termed an autoimmune disease and prominent examples include Coeliac disease, diabetes mellitus type-1 (IDDM), Hashimoto's thyroiditis, Graves' disease and rheumatoid arthritis (RA).\textsuperscript{3-4}

2. Arthritis

Arthritis (from Greek \textit{arthro-}, joint + \textit{-itis}, inflammation; plural: arthritides) is a chronic autoimmune disease of which the main characteristic is irreversible joint destruction.\textsuperscript{5-6} It is a group of conditions involving damage to the joints of the body. Rheumatic diseases are estimated to affect up to 1.1 \% of world’s population and these patients are often treated with steroids, Non-Steroidal Anti-Inflammatory agents (NSAIDs), Disease Modifying Anti-Rheumatic Drugs (DMARDs) and/or immunosuppressive drugs.\textsuperscript{7} Currently available therapy for the arthritis focuses on reducing inflammation of the joints with NSAIDs and steroids.

3. Types of arthritis

There are over 150 different forms of arthritides but the most common of them includes rheumatoid arthritis (RA), osteoarthritis (OA), spinal disorders and septic arthritis.\textsuperscript{8}

3.1 Rheumatoid arthritis

RA is a chronic immune inflammatory disease characterized by synovial hyperplasia, joint destruction and extra-articular manifestations with a significant impact on both morbidity and mortality. It affects 0.5-1 \% of the population in the industrialized world and commonly leads to significant disability and a consequent reduction in quality of life.\textsuperscript{9} It is two to three times more frequent in women than in men and can start at any age with a peak incidence between the fourth and sixth decade of life.\textsuperscript{10}

3.1.1 Etiology and pathogenesis of RA

The etiopathology of this condition is not fully understood. Many consider it to be an autoimmune disorder, although its exact cause is unknown. It is known that neutrophils, macrophages, synovial fibroblasts, T cells and B cells are involved in the mechanisms that drive the onset of RA.\textsuperscript{11} T cells, B cells and macrophages infiltrate the synovium and form discrete lymphoid aggregates, sometimes with ectopic germinal centers while
macrophage-like and fibroblast-like synoviocytes accumulate in the intima causing hyperplasia and secrete degradative enzymes. The difference between anatomy of normal and arthritic joints is shown in Fig. 1.1 below.

Fig. 1.1: Anatomy of normal and arthritic joints OA/RA

### 3.2. Osteoarthritis

In contrast to RA, OA is relatively noninflammatory degenerative joint disease occurring mostly in older persons and is characterized by the degeneration of articular cartilage, hypertrophy of bone at the margins and changes in the synovial membrane. OA is the most common joint disease affecting over 50% of the population over 65 years of age and 80% of the population over 75 years of age. The most common symptom of OA is pain often worsening with joint movements and improving at rest.

#### 3.2.1 Etiology and pathogenesis of OA

OA usually has a slow and insidious onset. Clinically, OA manifests in the form of gradual development of joint pain, joint stiffness and crepitus with motion, joint effusions and limitation of movement in the joints. Risk factors for the development and progression of OA include local biomechanical factors like obesity, joint injury, joint deformity and extensive sport participation as well as systemic factors including age, gender, ethnic characteristics, bone density and estrogen deficiency.

OA affects only one single or a few joints. The joints most frequently affected by OA, based on radiographic evidence in Caucasian populations are the knees (33% prevalence) followed by the hands (29.5%), feet (20.8%) and the hips (4.7%).
4. Arthritis and cartilage damage

4.1. Structure of articular cartilage

Articular cartilage is a specialized connective tissue resting on subchondral bone that covers the surfaces of diarthrodial joints. A mature articular cartilage is a heterogeneous tissue with four distinct regions: the superficial tangential (or gliding) zone, middle (or transitional) zone, the deep (or radial) zone and the calcified cartilage zone located immediately below the tidemark and above the subchondral bone.\textsuperscript{15} Joint cartilage, a connective tissue that consists of chondrocytes and their surrounding extracellular matrices plays an essential role in the mechanical cushioning of joints in postnatal locomotion.

![Diagram of Articular Cartilage](image.png)

\textbf{Fig. 1.2:} Articular cartilage anatomy and collagen arrangement

Damage to joint cartilage is likely to lead to long term joint problems. This is largely because cartilage does not have a direct supply of blood (avascular tissue) and thus cannot be quickly repaired naturally by the body. Joints are also particularly vulnerable to degeneration because it is common for the needs of their repair to outstrip the body's ability to produce new cartilage.\textsuperscript{16}

4.2. Biochemistry of cartilage

Cartilage is made up of water (70 \%) and type II collagen (20 \%) with proteoglycans and glycosaminoglycans (consisting mainly of aggrecan and chondroitin) produced by chondrocytes. Healthy joint cartilage distributes static and dynamic joint
loading and decreases friction. Sparsely distributed cartilage cells maintain the 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 OA include gradual proteolytic degradation of the matrix associated with increased synthesis of the same (or slightly altered) matrix components by the chondrocytes.\textsuperscript{17}

The major collagen in articular cartilage is type-II collagen, which accounts for >50% of its dry weight. As the second component of cartilage, aggrecan is a multidomain proteoglycan with several well-characterized functional regions. The core protein of aggrecan comprises of two \textit{N}-terminal globular domains G1 and G2 separated by the E1 domain followed by a more extended E2 domain and terminated by the third globular domain G3. The negatively charged groups in aggrecan are keratan sulfate and chondroitin sulfate in the E2 domain. A large amount of negative charges in this domain contributes to the stiffness of cartilage\textsuperscript{18}

4.2.1. Proteoglycans

Proteoglycans are huge complex molecules composed of proteins and sugars. They interlink with the collagen fibers forming a dense matrix or network inside the cartilage making it resilient so that it can stretch when we move and spring back into place. Proteoglycans also trap water from the tissues acting like a sponge giving cartilage the flexibility.\textsuperscript{17-19}

4.2.2. Glucosaminoglycans

The most abundant heteropolysaccharides in the body are the GAGs. These molecules are long unbranched polysaccharides containing a repeating disaccharide unit. The disaccharide units contain either of the two modified sugars \textit{N}-acetylgalactosamine (GalNAc) or \textit{N}-acetylglucosamine (GlcNAc) and an uronic acid such as glucuronate or iduronate. GAGs are highly negatively charged molecules, with extended conformation that imparts high viscosity to the solution.\textsuperscript{17}

The specific GAGs of physiological significance are hyaluronic acid, dermatan sulfate, chondroitin sulfate, heparin and heparan sulfate and keratan sulfate. Hyaluronic acid is unique among the GAGs in that it does not contain any sulfate and is not found covalently attached to proteins as a proteoglycan. Hyaluronic acid polymers are very large (molecular weights of 100,000-10,000,000) and can displace a large volume of water. This property makes them excellent lubricators and shock absorbers\textsuperscript{20} The composition of
various GAGs and the linkage they contain have been shown in Table 1.1 below and in Table 1.2 the location of various GAGs has been given.

**Table 1.1: Composition of GAGs and linkage**

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Type of sugar</th>
<th>Composition</th>
<th>Linkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hyaluronates</td>
<td>D-glucuronate + GlcNAc</td>
<td>(1, 3)</td>
</tr>
<tr>
<td>2</td>
<td>Dermatan sulfates</td>
<td>L-iduronate (many are sulfated) + GalNAc-4-sulfate</td>
<td>(1, 3)</td>
</tr>
<tr>
<td>3</td>
<td>Chondroitin sulfates</td>
<td>D-glucuronate + GalNAc-4- or 6-sulfate</td>
<td>(1, 3)</td>
</tr>
<tr>
<td>4</td>
<td>Heparan sulfates</td>
<td>D-glucuronate-2-sulfate (or iduronate-2-sulfate) + N-sulfo-D-glucosamine-6-sulfate</td>
<td>(1, 4)</td>
</tr>
<tr>
<td>5</td>
<td>Keratan sulfates</td>
<td>Galactose + GlcNAc-6-sulfate</td>
<td>(1, 4)</td>
</tr>
</tbody>
</table>

*GlcNAc* = Glucosamine *N*-acetyl, *GalNAc* = Galactosamine *N*-acetyl

**Table 1.2: Types of GAGs and their location**

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>GAGs</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hyaluronates</td>
<td>Synovial fluid, ECM of loose connective tissue</td>
</tr>
<tr>
<td>2</td>
<td>Dermatan sulfates</td>
<td>Skin, blood vessels, heart valves</td>
</tr>
<tr>
<td>3</td>
<td>Chondroitin sulfates</td>
<td>Cartilage, bone, heart valves</td>
</tr>
<tr>
<td>4</td>
<td>Heparan sulfates</td>
<td>Basement membranes, components of cell surface</td>
</tr>
<tr>
<td>5</td>
<td>Keratan sulfates</td>
<td>Cornea, bone, cartilage,</td>
</tr>
<tr>
<td>6</td>
<td>Heparin</td>
<td>Component of intracellular granules of mast cells lining the arteries of the lungs, liver and skin</td>
</tr>
</tbody>
</table>

4.3. Cartilage damage and repair

A large range of motion and the demands of constant use especially bearing weight can damage the cartilage of the joints. Not just age, but sports and accidents can lead to similar damage.

In a person with joint issues, cartilage is destroyed faster than it is synthesized. The key limiting step on the synthesis side is production of GAGs for which glucosamine is the basic building block. Glucosamine is a natural substance found in the body and made from the combination of a sugar (glucose) and an amine derived from the amino acid glutamine. Chondrocytes are cells responsible for the repair and regeneration of cartilage tissues, both its removal when damaged and its synthesis.
Enzymes produced by the chondrocytes tear down damaged or old cartilage, just as proteoglycans synthesized by the chondrocytes renew cartilage. Both steps are necessary for joint health and a balance needs to be maintained. Various molecules involved in the catabolic and anabolic processes of the chondrocytes are shown in Table 1.3

A balance between anabolic and catabolic signals maintains the homeostasis of cartilage. In normal cartilage the balance between anabolism and catabolism is equivalent. In OA cartilage, catabolism becomes more dominant than anabolism leading to the degradation of the cartilage.\textsuperscript{17} Fig. 1.3 and 1.4 provides diagramatic and schematic view of the signaling factors affecting cartilage homeostasis respectively.

Table 1.3: Molecules involved in the catabolic and anabolic processes of the chondrocytes

<table>
<thead>
<tr>
<th>No</th>
<th>Source</th>
<th>Catabolism</th>
<th>Anabolism</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Proteolytic Enzymes</td>
<td>Collagenases-I, II, III</td>
<td>TIMPs</td>
<td>19, 69, 72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stromelysin, Aggrecanase</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cathepsin-K, COX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cytokines and Growth Factors (GF)</td>
<td>IL-1, IL-17</td>
<td>TGF-(\beta)</td>
<td>35, 56-57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNF-(\alpha)</td>
<td>IGF, bFGF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BMPs</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Nitric oxide and Prostaglandins</td>
<td>NO</td>
<td>--</td>
<td>19, 35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostaglandin E2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*TIMPs: Tissue inhibitors of metalloproteinase

As the most abundant bone cell type, osteocytes are mature osteoblasts located in the bone matrix. Normally bone resorption by osteoclasts and bone formation by osteoblasts are well balanced to maintain the function of the skeleton. However, under pathological conditions (e.g., RA and OA) such balance is disturbed. Bone resorption however is mostly mediated by osteoclasts.

It is believed that various cytokines released during development of the disease help to recruit osteoclasts to the sites of destruction. As osteoclasts start the bone resorption process they will secrete cathepsin-K to cleave the type-I collagen triple helix fibrils and other bone proteins.\textsuperscript{24}
Fig. 1.3: Anabolic and catabolic signaling factors affecting cartilage homeostasis, involvement of the synovium in OA pathophysiology and products of cartilage breakdown that are released into synovial fluid.


Fig. 1.4: Regulators of cartilage metabolism
5. Diagnosis of arthritis

Arthritis is a complicated disease and an accurate diagnosis is required for proper treatment of arthritis. As mentioned earlier with over 150 types of arthritis, early symptoms can overlap and diagnosis can be difficult but this is beyond the scope of this chapter. Here, diagnosis of RA and OA mainly has been focused.

5.1. Diagnosis of RA

RA can be difficult to diagnose. Many other conditions resemble it and its symptoms can develop insidiously. In a clinical diagnosis patients commonly report pain and stiffness in multiple joints. One third of the patients initially experience symptoms at just one location or a few scattered sites.

Table 1.4: Summary of the tests and findings associated with RA.25-26

<table>
<thead>
<tr>
<th>SR. No</th>
<th>Laboratory Test*</th>
<th>Associated Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C-Reactive protein</td>
<td>Typically increased to &gt;0.7 pg/ml.</td>
</tr>
<tr>
<td>2</td>
<td>ESR</td>
<td>Often increased to &gt;30 mm per hour.</td>
</tr>
<tr>
<td>3</td>
<td>Hemoglobin/hematocrit</td>
<td>Slightly decreased; Hb average 10 g per dL normochromic, normocytic or microcytic anemia.</td>
</tr>
<tr>
<td>4</td>
<td>Liver function</td>
<td>Normal or slightly elevated alkaline phosphatase</td>
</tr>
<tr>
<td>5</td>
<td>Platelets</td>
<td>Usually increased</td>
</tr>
<tr>
<td>6</td>
<td>Radiographic findings of involved joints</td>
<td>May be normal or show osteopenia or erosions near joint spaces in early disease.</td>
</tr>
<tr>
<td>7</td>
<td>Rheumatoid factor</td>
<td>Negative in 30 % of patients early in illness; can be positive in other processes e.g., lupus; scleroderma</td>
</tr>
</tbody>
</table>

* Recommended for initial evaluation for RA

In RA, antibodies that collect in the synovium of the joint are known as rheumatoid factor. Table 1.4 enlists various major tests and findings associated with RA.

5.2. Diagnosis of OA

OA requires some special mention because it is the most common form of arthritis. It differs from RA in several important respects as described below:

- OA usually occurs in older people
- It is located in only one or a few joints. (In fact OA is probably most often confused with RA if it affects multiple joints in the body)
- The joints are less inflammed
- Progression of pain is almost always gradual
The diagnosis of OA is largely made by obtaining a detailed history and conducting a complete physical examination. Clinically indicated laboratory tests may include tests for erythrocyte sedimentation rate and rheumatoid factor. Synovial fluid analysis may be conducted to help exclude other diagnoses. Radiographs can provide objective evidence of the disease.

6. Arthritis treatment

Arthritis causes significant morbidity and mortality and must be treated aggressively from the time of its diagnosis. There is no known cure for arthritis or means of preventing it. Optimal management requires early diagnosis and timely introduction of agents that reduce the probability of irreversible joint damage. Other studies suggest that early aggressive treatment may alter the course of the disease and most rheumatologists favor aggressive treatment early in the course of the disease.

6.1. Treatment of RA

The principles of management of RA are to relieve pain, prevent deformity and maintain normal functions. Therapeutic goals include preservation of functions and quality of life, minimization of pain and inflammation, joint protection and control of systemic complications. Drug therapy for RA rests on two principal approaches, symptomatic treatment with NSAIDs and DMARDs. Fig. 1.5 outlines possible approaches to the treatment of a patient with RA.

Fig. 1.5: Approaches to the treatment of RA
Joint destruction in RA begins within a few weeks of onset of symptom and early treatment decreases the rate of disease progression. Therefore it is imperative to diagnose the disease and initiate the treatment as soon as possible. If not treated on time RA may develop various complications such as anemia, cancer, cardiac complications, fistula formation rheumatic nodules etc. Patients with RA must be managed by a multidisciplinary team in which the general practitioner and rheumatologist are pivotal. Patient’s involvement in decisions on therapeutic options is increasingly important.

6.1.1. Education

Education has an important role; it provides information on the disease and its therapies giving patients a realistic outlook and allowing them to be involved in therapeutic decisions.

6.1.2. Exercise

Much of the pain and stiffness in RA arises from periarticular tissues such as muscles and tendons. These symptoms are amenable to exercise to some extent and it is important that all patients with RA regularly perform a general exercise programme to improve and maintain general fitness and maintain muscle bulk around the joints.

6.1.3. Dietary advice

Dietary advice is often sought and should be provided appropriately. Dietary issues include weight reduction and the addition of fish oils or evening primrose oil. Fish oil substitutes have enabled reduction or discontinuation of NSAIDs in RA patients.

6.1.4. Pharmacotherapy

Once the diagnosis of RA has been confirmed, treatment with drugs that retard joint destruction and reduce disability should be commenced promptly in almost all cases. Pharmacotherapy for rheumatoid arthritis generally involves an NSAID for control of pain, with selective use of low-dose oral or intra-articular (IA) glucocorticoids and initiation of a DMARD. Other analgesics also may be used; NSAIDs have no effect on long-term disability but provide symptom relief.

6.1.4.1. Analgesics and NSAIDs

Analgesics reduce pain and NSAIDs lessen pain and stiffness. Both groups of drugs are used widely to control symptoms of rheumatoid arthritis. Evidence for use of analgesics is modest but uncontroersial support for use of NSAIDs is considerably stronger. NSAIDs have lost their historical role as first-line treatment because of concerns about their limited effectiveness, inability to modify the long-term course of disease and gastrointestinal and cardiac toxic effects.
NSAIDs interfere with a small segment of the inflammatory cascade only, namely prostaglandin generation by cyclooxygenases (COXs), but do not interfere with the underlying immuno-inflammatory events or retard joint destruction. Combinations of two or more NSAIDs should be avoided since they are no more effective and may have additive adverse effects. Since the present work pertains to site specific chemical delivery of some NSAIDs it is in order to discuss NSAIDs, their classification, mechanism of action and adverse effects etc. in detail as discussed in Section-7

6.1.4.2. DMARDs

In contrast to NSAIDs, DMARDs ‘modify’ the disease process in all these respects and once DMARDs are effective no further symptomatic therapies are needed. All patients whose RA remains active despite adequate treatment with NSAIDs are candidates for DMARD therapy. Active RA may lead to irreversible joint damage even in the early months of the disease; while NSAIDs and glucocorticoids may alleviate symptoms; joint damage may occur and progress.

Currently DMARDs such as adalimumab, methotrexate, azathioprine, infliximab, etanercept etc. are used for the treatment of arthritis.

6.1.4.3. Glucocorticoids

Low-dose oral glucocorticoids (<10 mg prednisone daily or equivalent) and local injections of glucocorticoids are highly effective for relieving symptoms in patients with active RA. Low dose glucocorticoids appear to slow the rate of joint damage. The adverse effects of systemic glucocorticoids, especially when taken in higher doses for extended periods of time limit their use, however when administered by an experienced physician glucocorticoid injection of joints and periarticular structures is safe and effective. Injecting one or a few of the most involved joints in a patient early in the course of RA may provide local and even systemic benefits. The effects are sometimes dramatic but may be temporary. Prompt improvement from IA glucocorticoids helps to instill confidence in the patients impressing that the treatment can be effective. A patient who has flare in one or a few joints can be treated successfully by injection of the flaring joint or joints without requiring a major change in the prescribed regimen.

6.1.4.4 Biological agents for RA

Most of the biologic agents have been evaluated as single agent therapy (monotherapy) and thus have not yet been tested in combination with one another (e.g., anti-CD4 MAb combined with anti-TNF agents) or with currently used DMARDs. TNF inhibitors were the first licensed biological agents followed by abatacept, rituximab, and
tocilizumab. Various biological agents developed or under development are shown in Table 1.5

**Table 1.5:** Biologic agents that inhibit T cell function and have been evaluated in clinical trials in patients with RA

<table>
<thead>
<tr>
<th>No</th>
<th>Biologic Agent</th>
<th>Target Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Murine anti-CD4 MAb*</td>
<td>CD4+ T Cell</td>
</tr>
<tr>
<td>2</td>
<td>Chimeric anti-CD4 (depleting) MAb</td>
<td>CD4+ T Cell</td>
</tr>
<tr>
<td>3</td>
<td>CAMPATH-1H MAb</td>
<td>CDw 52</td>
</tr>
<tr>
<td>4</td>
<td>Murine anti-CD5 ricin toxin</td>
<td>CD5</td>
</tr>
<tr>
<td>5</td>
<td>Anti-CD7 MAb</td>
<td>CD7</td>
</tr>
<tr>
<td>6</td>
<td>Anti-IL-2 MAb</td>
<td>IL-2 receptor</td>
</tr>
</tbody>
</table>

*MAb: monoclonal antibody

6.1.4.5 Gene Therapy

Gene therapy provides another avenue for treating autoimmune disorders. The goal is to increase local expression of anti-inflammatory molecules involved in synovial tissue. Candidate molecules to date have included cytokine antagonists such as IL-1Ra, sTNFR, IL-10, IL-4, and sIL-1R. The feasibility of this approach has been tested in animal models using IL-1Ra.34

6.1.4.6 Surgery

Even if joint inflammation is successfully controlled or eliminated with medication, patients with chronic RA have unacceptable pain and/or limitation of function because of structural joint damage or functional impairment is severe, then surgery should be considered.25 Synovectomy and arthroplasty have significant roles in the overall management of RA. Hip and knee arthroplasty and forefoot reconstruction can significantly improve mobility in patients with damaged joints. Arthrodesis may be helpful for unstable joints (e.g. wrist, atlantoaxial joint).28

6.2. Treatment of OA

The aims of treatment of OA are patient education, pain control and improvement of function. The treatment interventions in OA include non-drug therapy, drug therapy, and surgical treatment as shown in Fig. 1.6.17 Though each therapy has respective
advantages and efficacy to some degree, there is no fundamental therapy aimed at repairing the underlying molecular problem.

**Fig. 1.6: Approaches to the treatment of OA**

### 6.2.1. Non-drug therapy

Formal patient education by any member of a multidisciplinary team should be an initial part of management of OA. Physical therapy is another mainstay in the treatment of OA; the mechanisms of which have not been clarified yet. Physiotherapists use two major approaches: muscle strengthening programs specific for certain joints and general aerobic conditioning.

### 6.2.2. Drug therapy

Paracetamol is a common first choice drug among several analgesics. Use of this medication is supported by the excellent safety record and low cost of paracetamol relative to NSAIDs. Especially in the elderly it is safe and well tolerated.\(^{35}\) Paracetamol/opiate combinations such as coproxamol may be used if paracetamol alone is unhelpful. Stronger opiates should be avoided if at all possible.

Both the ACR and European League against Rheumatism guidelines (ELR) recommend paracetamol alone as an initial therapy. NSAIDs have been found to have equal efficacy to paracetamol in most patients with OA.\(^{42}\) However recent data suggest that NSAIDs may be better than paracetamol for symptomatic relief of OA in large joints. Novel therapeutic agents have been developed that act as specific inhibitors of the cyclooxygenase-2 isoform (COX-2 inhibitors). Topical treatment is an additional option for patients with OA who have inadequate pain relief or who cannot tolerate systemic
therapy. The two types of topical agents in the treatment of this disorder are NSAIDs and capsaicin.\textsuperscript{37} A recent meta-analysis concluded that both agents are well tolerated and have significantly greater analgesic effects than placebo.

IA corticosteroids are widely used in the management of patients with OA of the knee, most commonly in those patients who have active inflammation. Patients with a painful flare of OA of the knee may benefit from IA injection of a corticosteroid such as methylprednisolone (Medrol) or triamcinolone (Aristocort).\textsuperscript{38} When a joint is painful and swollen, short term pain relief can be achieved with aspiration of joint fluid followed by IA injection of a corticosteroid. A joint should not be injected with more than three or four times in one year because of the possibility of cartilage damage from repeated injections.\textsuperscript{39}

Other choice is use of hyaluronic acid, a high molecular weight polysaccharide and a major component of synovial fluid and cartilage. Several studies suggest that IA hyaluronic acid shows superior pain relief to placebo and equivalent relief to corticosteroid injections but with a greater duration of action.\textsuperscript{40}

\textbf{6.2.3. Surgical treatment}

In majority cases surgical treatment of OA is considered only after failure of non-surgical treatments. Four categories of non-biological procedures are considered in surgical management: osteotomy, arthroscopy, arthrodesis and arthroplasty.\textsuperscript{41} For most patients, especially in the elderly ones total joint arthroplasty is highly successful and the therapeutic effects will last for the remainder of the patient’s expected lifespan.

\textbf{6.2.4. Future direction for OA treatment}

An approach that incorporates tissue engineering is one of the most promising of OA therapies.\textsuperscript{42} Use of viral vectors is a viable method to induce anabolic genes into sampled cells to achieve cartilage development with high efficiency.\textsuperscript{26} Scaffolding of natural polymers has been used to shape cartilage appropriately.

\textbf{7. Non-Steroidal Anti-inflammatory Drugs (NSAIDs)}

NSAIDs, is an important therapeutic class of drugs used to suppress pain and inflammation in cases of RA and other inflammatory diseases.\textsuperscript{43} In 1970s a scientific breakthrough occurred with the elucidation of the molecular mechanism of aspirin and other NSAIDs.\textsuperscript{44} Since then heterogeneous groups of compounds often unrelated chemically (although most of them are organic acids) have been introduced as NSAIDs. These anti-inflammatory substances block the biosynthesis of prostaglandins which contribute to a variety of physiological and pathophysiological functions.
7.1. Classification of NSAIDs

NSAIDs can be broadly classified on the basis of their selectivity for COX enzyme.45

7.1.1. Non-selective acidic COX inhibitors: There can be further sub-classified on the basis of chemical structure e.g. aspirin, paracetamol, indomethacin, ibuprofen, naproxen etc.

7.1.2. Selective COX-2 inhibitors: e.g. etodolac, nimesulide, celecoxib, etoricoxib etc.

7.2. Pharmacological actions and therapeutic uses of NSAIDs

All NSAIDs including selective COX-2 inhibitors are anti-inflammatory, antipyretic and analgesic. One important exception is acetaminophen which is antipyretic and analgesic but is largely devoid of anti-inflammatory effect. Other uses of NSAIDs include treatment of cancer. Prostaglandin E₂ has been implicated in the humoral hypocalcaemia associated with some neoplasm and treatment with NSAIDs can effectively suppress serum calcium levels in some cancer patients. Excessive production of renal PGs has been implicated in the pathogenesis of some of the metabolic abnormalities in the Bartter’s syndrome and NSAIDs have been found to be useful in the treatment of this disorder.44

7.3. Mechanism of action of NSAIDs

The major mechanism by which NSAIDs elicit their therapeutic effect is inhibition of PG synthesis. NSAIDs work by interfering with the cyclooxygenase pathway. The normal process begins with arachidonic acid; this acid is converted by the enzyme cyclooxygenase (COX) to synthesize different prostaglandins (PGs).44

7.4. Side effects of NSAIDs

Side effects of NSAIDs are due to the inhibition of COX-1 enzyme. The widespread use of NSAIDs has meant that the adverse effects of these relatively safe drugs have become increasingly prevalent. Some major adverse effects of NSAIDs include gastrointestinal toxicity, renal ADRs, photosensitivity, blockade of platelet aggregation, hepatic complications and inhibition of uterine motility etc.46

8. Approaches used to reduce toxicity of NSAIDs

There are several ways in which the risk of side effects of NSAIDs can be reduced. Some of these are given below:

- By prodrug approach
• Using selective COX-2 inhibitors
• Using lower-risk NSAIDs such as ibuprofen at doses of less than 1,600 mg per day
• Using enteric-coated aspirin (has a lower risk of side effects)
• Using misoprostol which protects the stomach lining when taken in addition to NSAIDs
• Incorporating proton pump inhibitors: Omeprazole, Ranitidine, Cimetidine, Famotidine etc.
• By parenteral administration of NSAIDs
• By targeted drug delivery of NSAIDs

9. Cartilage targeted drug delivery in arthritis

It has been first shown by Freudenberg et al.\textsuperscript{47} that dried preparations of cartilage can take up certain cations from solution and this observation was further proved by Boyd et al.\textsuperscript{48} who showed that the equivalent capacity of the cartilage to bind sodium, calcium, and barium ions \textit{in vitro} and the mechanism involved is the same in each case and that it may be regarded as a stoichiometric chemical reaction. The binding of calcium by cartilage was shown to be an ion exchange reaction.

The close correlation between binding capacity and sulphate content in both preparations implicates chondroitin sulphate as the principal binding agent. Since sulfate is present as the ester sulfate it can account for only one half of the total binding capacity for the cations. Although the protein carboxyl groups have been shown to bind cations and could conceivably account for the total binding capacity of the cartilage.\textsuperscript{49} The experiment from Klotz et al. shows no binding of phosphate unless cartilage contains appreciable amounts of calcium in which case phosphate is taken up by the cartilage until the Ca: P ratio is approximately that of hydroxyapatite.\textsuperscript{49}

These findings suggest that conflicting results obtained by Roche and Deltour et al.\textsuperscript{50} that cartilage first binds phosphate followed by a binding of calcium was clear from the experiment done by Klotz et al. and it could be concluded that when mineral content (cations) is high in cartilage then mineral itself may absorb the ions (anions), and this phenomenon may be responsible for the results obtained by Roche and Deltour et al.\textsuperscript{48}

This finding was further supported by the fact that quaternary ammonium compounds like hexamethonium (1) and decamethonium (2) accumulated preferentially in certain avascular cartilaginous tissues on intramuscular injection\textsuperscript{51}, whereas little of them
were found in blood rich bone marrow. It has been postulated that these quaternary ammonium compounds are localized in the cartilage tissues, probably by virtue of ionic interactions with cartilaginous tissues. Thus it is concluded that both the mono and diquaternary compounds which exist exclusively in the charged form in blood are localized in the cartilage by ionic interactions with polyanionic acid mucopolysaccharides. However diquaternary compounds achieved higher concentrations in cartilage than the monoquaternary compounds; because energy of interaction of dicationic compounds is double than monocationic compounds.

These observations have been further supported by Maurizis et al.\textsuperscript{,52} and it was concluded that localization of quaternary ammonium compounds such as pyrimidoxime (3) and \textit{N,N}-trimethylene bis(pyridinium-4-aldoxime) dibromide (TMB4) (4) in the cultured proteoglycan suspension was due to ionic interaction. This factor together with their poor lipophilicity can explain their high selectivity for the cartilaginous tissues as opposed to other proteoglycan containing tissues such as skin.

This idea has been further extended to the site specific delivery of antirheumatic agent \textit{D}-glucosamine (5) to the cartilaginous tissues by conjugating it with some
quaternary ammonium groups. $^{14}$C-Labeled quaternary ammonium-glucosamine conjugates (6 and 7) were prepared by Giraud et al. and their biodistribution in rats were studied.$^{53}$

It was reported that introduction of a quaternary ammonium moiety in $D$-glucosamine (5) a compound which already exhibited a special tropism for cartilage, allowed the molecule to be carried more selectively to the cartilagenous tissues soon after intravenous injection in rodents. Both the compounds (6 and 7) have been reported to have higher affinity for cartilaginous tissues than for the unconjugated $^{14}$C-$D$-glucosamine (5).

![Chemical structures](image)

Literature survey also revealed that introduction of a quaternary ammonium function on oxicam structures greatly increased their affinity for the cartilaginous tissues. Analog of oxicam NSAIDs like piroxicam (8) and propoxicam (10), in which the active group was linked to quaternary ammonium function [piroxicam-$N^+$ (9) and propoxicam-$N^+$ (11)] were synthesized and labeled with radioactive probes. Pharmacokinetic study conducted on rats showed that these molecules were able to highly concentrate in joint cartilage.$^{54}$

Previous work from this laboratory$^{55}$ also reported selectivity of NSAIDs such as 6-MNA (12) towards cartilage increased when cationic group was present in structure (13). The above compound (13) was also evaluated for site specificity and it was found
that it was localized in inflammed areas and intensely accumulated in the cartilage as compared to parent NSAIDs (12) following i.v. administration. So from the above literature reports we can conclude that cationic molecules possess affinity towards anionic cartilage hence advantage could be taken of this property to develop various chemical delivery systems of NSAIDs or their delivery systems for the treatment of arthritis.

References
4. www.wikipedia.org


