

# Osteoarthritis

## What is osteoarthritis?

Osteoarthritis (OA) is the term used for a family of conditions involving the degeneration of cartilage and the proliferation of new bone and connective tissue. In late stage cases, abnormal bone growth causes visible bumps and ridges around the joints. OA can affect most joints, including the spine, but the disease is more common in the knees, hips, feet and hands. Most cases of osteoarthritis have no known cause and are referred to as primary osteoarthritis. When the cause of the osteoarthritis is known, the condition is referred to as secondary osteoarthritis.

Nodal OA, affecting the finger joints and which occurs predominantly in middle-aged women, is clinically distinct from, for example, OA of the knees, which is often related to obesity and shows a more even sex distribution. Symptoms depend on the part affected, but include pain, stiffness and loss of function. Pain can become severe in the later stages of OA, when replacement of the joint affected may become necessary.

## Who does OA affect?

By the age of 65, 80 per cent of people have evidence of OA in X-rays, although only about 25 per cent have symptoms. Recent estimates have put the number of people in the European Union suffering from OA at almost 15 million, but this may be an underestimate.

It isn't clear what causes osteoarthritis in most cases. Scientists suspect that it is a combination of factors, including being overweight, the ageing process, joint injury or stress, heredity, and muscle weakness. After the age of 55, OA occurs more frequently in females. All races appear equally affected. A higher incidence of OA exists in the Japanese population.

## Present treatments:

Aside from weight reduction and avoiding activities that exert excessive stress on the joint cartilage, there is no specific treatment to halt cartilage degeneration or to repair damaged cartilage in OA. Treatments today are solely concerned with managing symptoms such as pain. In many patients, mild pain relievers may be sufficient.

Medicines to relax muscles in spasm might also be given temporarily. Pain-relieving creams applied to the skin over the joints can provide relief of minor arthritis pain. Treatments which are used for the relief of the pain of OA also include anti-inflammatory lotions and patches. Exercises to build muscle are useful in people who are still active, and in cases where simple analgesics do not suffice, non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed for pain control; corticosteroid injections into the joint can help in acute cases.

**Osteoarthritis causes pain and stiffness of the joints. Over the years, many medicines have been developed which offer pain relief to patients and help them stay mobile and independent.**

**By understanding the disease process, there is the promise of even better medicines to come.**



In addition, various preparations are available for injection to improve the elasto-viscous properties of the synovial fluid in the joints, but this does not alter the course of the disease.

NSAIDs inhibit an enzyme called cyclo-oxygenase (COX), blocking the formation of inflammatory prostaglandins (PGs). COX exists in two forms: COX-1 and COX-2. Prostaglandins produced by COX-2 are inflammatory and damage the gut, producing gastric ulcers and bleeding, but those from COX-1 have a protective effect.

Some of the older NSAIDs inhibit COX-2 preferentially but are not entirely selective. In general, they have a lower risk of gastric ulcer formation than NSAIDs, which preferentially inhibit COX-1. Several truly COX-2 selective NSAIDs have been available in Europe for some years. They should be given preferably to patients with a risk of developing stomach ulcers and other complications which arise with older NSAIDs.

### **What's in the development pipeline?**

Additional selective COX-inhibitors are being studied for use in OA. These are second generation compounds with even better pharmacological profiles. Injectable formulations, in the form of pro-drugs of existing COX-2 molecules will be of particular interest.

Another type of NSAID, which is currently in Phase 3 trials has been shown to inhibit not only cyclo-oxygenase, but also the enzyme 5-lipoxygenase, which produces leukotrienes that cause pain and inflammation. The substance controls pain and inhibits platelet aggregation and has been found to be of value in rheumatoid arthritis as well as in OA.

Further new treatment approaches are also being studied by various research groups, such as an inhibitor of an enzyme that may affect bone destruction, an anti-inflammatory compound, and an oral form of calcitonin.

The possibility of modifying disease progress is being investigated in studies that use a bisphosphonate compound. Microscopic fractures of bone at the joint surface have been suggested as a possible underlying cause of OA and bone cysts and sclerosis are seen in advanced stages of the disease.

As bisphosphonates have been shown to prevent bone remodelling in osteoporosis, there is hope that this approach might slow disease progress in OA too. Although reduction in pain has so far not been found, the compound reduced the level of a marker of bone turnover that is associated with the progression of osteoarthritis.

Research scientists have found that certain antibiotics can decrease inflammation inside affected joints. Antibiotics also block the proteins that play a role in the breakdown of the cartilage. Early studies of the antibiotic doxycycline have shown that the compound was able to slow the progression of cartilage degeneration in the knees of patients with OA. More studies are needed to determine the significance of this interesting finding.

### **The longer-term future**

While current medications can relieve pain and improve joint mobility, they cannot stop OA from progressing and further damaging the joints. Experiments and investigations into new medicines that could slow, stop or even reverse joint damage are under way.

Areas of investigation include compounds that interfere with inflammatory proteins called cytokines. These send signals to cells to cause the inflammation which plays a role in joint damage. OA is not typically thought of as an inflammatory dis-

ease, but researchers have found that people with OA have higher levels of inflammatory cells in their joints than are found in the normal population.

Treatments aimed at inflammatory cytokines include compounds that block the receptors that decode the inflammation-causing signals sent by such cytokines. Researchers are testing whether injecting cytokine-blocking agents into a joint can prevent damage from OA. Another approach would be a molecule that blocks only a specific part of a cytokine. So far, researchers have found that this principle may control OA pain, but more study is needed to determine if it can stop joint damage.

The long-term goal for research in OA must be medicines that modify disease progress. There is research underway to find inhibitors of aggrecanase, an enzyme that breaks down aggrecan, a major component of healthy cartilage. This programme is still at an early pre-clinical stage. Other investigations are directed towards the discovery of inhibitors of matrix metalloproteinase enzymes which are also involved in the breakdown of joint membranes in arthritic diseases.

Scientists are also trying to find new compounds that target specific joints to treat osteoarthritis of the knee or of the hand, for example. Also of interest are substances that during long-term therapy do not show the blood-pressure raising effect of NSAIDs that may be responsible for the increased risk of heart problems.

Finally, the food supplement glucosamine sulphate, a molecule involved in the natural production of cartilage, has been shown to have some effect in controlling mild to moderate pain in people with OA of the knee. However, it is not at present clear that this substance will be developed for formal regulatory approval.



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