

# Osteoarthritis

Your path to personal treatment



Endogenous immune proteins

- fight the causes of osteoarthritis inside the joint
- protect joint cartilage
- improve joint mobility

# Content

- 1 Joint pain – something CAN be done
- 2 Osteoarthritis can strike anyone
- 3 Causes of osteoarthritis
- 4 The amazing knee joint
- 5 Cartilage – your natural shock absorber
- 6 Early symptoms of osteoarthritis
- 7 Stages of joint disease
- 8 Pain: your body's alarm signal
- 9 Molecular orthopedics
- 10 "Bad proteins" destroy cartilage
- 11 "Good proteins" protect cartilage
- 12 Treatments for osteoarthritis
- 13 Orthokine<sup>®</sup>-therapy
- 14 When is Orthokine<sup>®</sup>-therapy indicated?
- 15 What can you expect as a patient?

# Joint pain – something CAN be done

In every day life, being independent and active as we grow older is an ideal that most of us strive for. Joint pain and back pain interfere with our ability to go about our daily activities and to participate in sports and other recreational and professional activities. Many sports, such as jogging, golf or skiing, put a great deal of stress on the joints. It is therefore extremely important that our joints continue to function smoothly and without pain into advanced age. Mobility is a major determinant of our quality of life.

Joint problems are frequently caused by the degeneration of cartilage. As the cartilage breaks down, pain and restricted mobility ensue. Osteoarthritis, one of the most widespread causes of pain and disability in the Western world, has set in.

As common as degenerative joint disease is, little is known about the underlying causes. Conventional treatment, in a nutshell, has been limited to reducing the pain for as long as possible. Finally, when pain control is no longer effective, the damaged joint is surgically replaced with an artificial one.

Is it possible to influence the disease mechanisms that cause osteoarthritis? What can be done to slow or even stop the degenerative processes altogether?

These are the problems Molecular Orthopedics is concerned with. The goal of this discipline is to decode the language of the cells, to better understand diseases of the musculoskeletal system and to develop new treatment approaches based on knowledge of the biological causes underlying them.

One of these treatment approaches is the Orthokine®-therapy, which was developed by two German medical researchers, orthopedist Dr. Peter Wehling and molecular biologist Dr. Julio Reinecke of Düsseldorf, in collaboration with Prof. Chris Evans of Harvard University and Prof. Paul Robbins of the University of Pittsburgh. In Orthokine®-therapy, immune proteins that fight pain and inflammation are produced from the patient's own blood. They are referred to as endogenous immune proteins, meaning that they are derived from or originate within the patient's own body.

These immune proteins – blood proteins that play a role in the functioning of the immune system – have the ability to protect cartilage and improve joint mobility. While this treatment is used primarily for osteoarthritis of the knee, hip and other joints, the same approach can also be used to treat back pain, with excellent results.

University hospitals both in Germany and abroad have had positive results with these new therapies. Clinical studies show that treatment of arthritis and back pain with Orthokine® is safe and effective.

The purpose of this brochure is to give patients up-to-date and accurate information about modern treatment options for osteoarthritis. The more patients know about the rationale for various methods of treating their disease, the better the treatment outcomes. If you have recently been diagnosed with osteoarthritis, we hope that the information herein will allow you to face the future more optimistically and look forward to enjoying good health, vitality and an active lifestyle into old age.

# Osteoarthritis can strike anyone

Osteoarthritis is part of the natural aging process that affects us all, as it is normal for the cartilage in the joints to break down over time. Osteoarthritis often develops very slowly over many years, and only becomes painfully debilitating when damage to the joint has already occurred. Osteoarthritis can affect any of the body's joints, particularly the knee, hip and hand joints, as well as the joints of the spine.

Up to 10% of the population in the developed countries suffer from osteoarthritis, with the knee being the most frequently affected joint. In recent studies, ten percent of people over the age of 55 reported pain and stiffness in their knees, and had x-rays which showed signs of degeneration of the knee joint.

Osteoarthritis of the knee and hip joints are among the top ten complaints diagnosed by orthopedists. They are among the 30 most frequent disorders for which hospitalization is required. In 2004, more than seven billion euros were spent in Germany alone for the treatment of osteoarthritis. Degenerative joint and spine disease also accounts for a considerable portion of all cases of disability, early retirement and rehabilitation, and as such is one of the greatest contributors to lost productivity out of all chronic diseases.

## Risk Factors

- sports injuries
- repetitive overuse, often related to work
- lack of exercise
- obesity
- bone fractures
- joint inflammation
- bone diseases
- neurological disorders
- metabolic diseases, e.g. diabetes
- congenital deformations, such as bowlegs or knock-knees
- genetic factors



# Causes of osteoarthritis

Osteoarthritis can be triggered by a variety of factors such as excessive stress on joints due to over-use, poor posture, musculoskeletal misalignment or sports injuries.

It affects mainly older people or people whose work involves hard physical labor or repetitive actions, as well as athletes and people who are overweight. In the case of athletes, wear and tear on the joints is caused by pushing the body to its limits repeatedly; in the case of obese people, it is caused carrying by excess weight. Deformations such as bowlegs and knock-knees can also lead to chronic strain, which in turn leads to joint degeneration. Furthermore, as we age, the layer of cartilage that cushions the joint generally loses water and elasticity.

Along with these mechanical processes, inflammation also plays a role. Pieces of cartilage may break off and float around in the joint, irritating the synovial membrane that forms the inner lining of the joint capsule. This causes the joint to become inflamed and swell up. This is sometimes referred to as "inflammatory arthritis." The inflammatory changes to the

synovial membrane prevent nutrients from entering the cartilage, thereby further accelerating the disease process.

Thus, there are risk factors that may contribute to osteoarthritis. In the early stages at least, osteoarthritis is in many cases a natural result of the body's aging process. But since not everyone ages in the same way, onset and severity of the condition vary widely from one person to another.

## At a glance

- Osteoarthritis is a chronic illness of the joints and the spine
- It can affect any joint in the body
- The knee is particularly susceptible to osteoarthritis
- Damage tends to begin within the articular cartilage
- Cartilage: a tissue without blood vessels

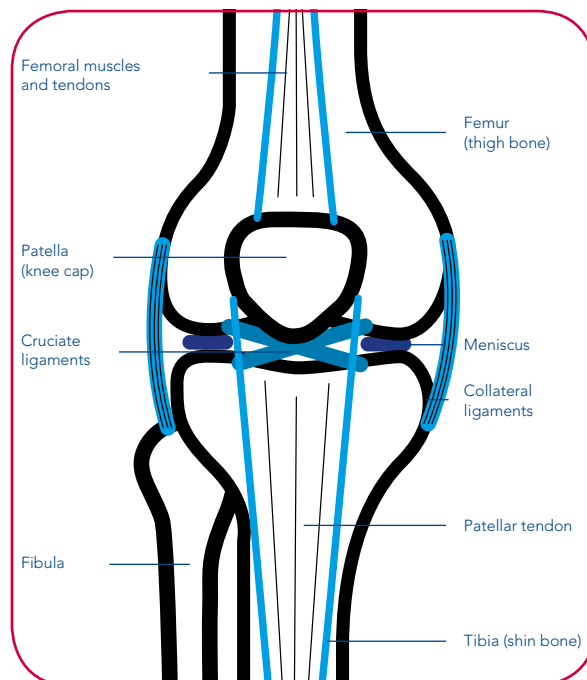


# The amazing knee joint

Although we are not consciously aware of it, our knee joints move thousands of times a day, absorbing abrupt shocks and sudden turns, carrying our body weight and keeping us stable. Given the multidirectional stresses and strains to which they are subjected, it is hardly surprising that the knees are more likely to be injured or wear out than any other joint in the body. So it makes sense to take a closer look at this hardworking joint.

## The largest joint in the body

The knee joint works like a hinge: it can bend (flex) and straighten (extend), and it also rotates slightly to allow the lower leg to turn in or out. The joint is formed by the ends of the femur (thigh bone) and the tibia (shin bone). The bone ends are covered by a layer of elastic cartilage (articular cartilage) that acts both as a bearing, allowing the bones to slide freely on one another, and as a shock absorber.



The knee joint is a complex structure and therefore vulnerable to injury and premature wear.

The ends of the bones and the cartilage are enclosed by an articular capsule. The inner layer of the capsule, the synovial membrane, contains many nerves and blood vessels. It produces a fluid (synovial fluid) that lubricates the joint and nourishes the cartilage.

Four ligaments connect the bones of the knee and provide stability to the joint:

- the medial and lateral collateral ligaments, located on the inner and outer sides of the joint, provide lateral stability when the knee is extended.
- the anterior and posterior cruciate ligaments cross in the center of the knee and limit the joint's rotational or twisting motions.

The meniscus, or meniscal cartilage, consists of two crescent-shaped cartilage discs, the medial (inner) and lateral (outer) menisci, that provide improved contact and cushioning between the ends of the femur and tibia bones. Most importantly, they distribute the weight of the body over a larger surface area and thus reduce the pressure on the articular cartilage. In a healthy knee, as much as 50 percent of the load on the joint is transferred to the menisci, thus reducing the pressure on the articular cartilage by half.

# Cartilage – your natural shock absorber

Injuries to cartilage, even small ones, weaken the cartilage and mean that even normal, everyday movements tend to cause additional strain on the remaining healthy cartilage. As a result, once the process of cartilage breakdown has begun, it has a tendency to spread.

## Cartilage – a very special tissue

Articular cartilage is unusual in that normal, healthy cartilage contains no blood vessels. This means that cartilage does not obtain vital nutrients from the blood as other body tissues do. It also means that cartilage cannot repair itself. Cartilage cells are supplied with nutrients solely from the synovial fluid that fills the spaces between the bones of the joint. In order to “feed” the layer of cartilage that covers the ends of the bones, it is vital that compression or stress on the joint be alternated with decompression or release of stress. This is why exercise is so important for keeping joints healthy. When pressure is exerted on the joint, used or waste matter is pressed out of the cartilage, and

during the decompression phase, the cartilage is bathed in new synovial fluid containing “fresh” nutrients. Also, because the “highways” of the blood vessels do not reach the cartilage, the immune system also has no direct contact with cartilage. Consequently, antigens and antibodies can only reach the joint indirectly. Drugs such as painkillers also cannot reach the cartilage by the normal route of the blood supply, and therefore higher concentrations are generally needed to be effective. However, substances that are injected directly into the joint itself circumvent this difficulty and are able to act directly on the tissues, including cartilage.

### Tips for healthy knees

- Even minor cartilage injuries should be taken seriously.
- Exercise keeps cartilage healthy by keeping the synovial fluid moving.





# Early symptoms of osteoarthritis

The first signs of osteoarthritis of the knee joint are stiffness or tightness in the knee, especially first thing in the morning or after extended periods of sitting or lying down. Pain upon straightening the knee joint is another warning signal.

As the person continues to move around and the knee joint is “warmed up,” the pain generally becomes less intense or disappears altogether. However, after extended periods of activity it will return.

Crunching or grinding sounds in the joint (crepitation) may also occur. Patients often report that the pain is worse during cold, damp weather.

As the disease progresses, pain may also occur at night or when the person is at rest. Going up – and especially down – stairs becomes difficult. Getting on or off a bus or climbing into or out of a car is painful.

Once deterioration of the cartilage layer has progressed to a certain point, the underlying bone will also be affected.

## Typical symptoms

- pain or stiffness upon getting up in the morning or after a long period of inactivity
- pain during or after activity
- limited range of motion
- swelling of the joint (swelling and heat usually indicate inflammation)
- pain at night or while sitting
- pain brought on by a change in weather
- crunching or crackling in the joint
- difficulty climbing or descending stairs



## Tips for healthy knees

- At the first signs of pain or stiffness in the joints, whether at night, first thing in the morning or during activity, seek the advice of your physician. The sooner treatment is begun, the better your chances of recovery!



# The stages of joint disease

## Early stage

In the early stage, cartilage damage is still minor. Fine cracks and contusions may be so small that they are often overlooked, but they weaken the cartilage and make it susceptible to further deterioration.

This damage, however minor, reduces the load-bearing surface area of cartilage in the joint. Healthy areas of cartilage are subjected to even greater loads.

At this stage, pain in the joint usually goes away with rest.

## Moderate stage

In the moderate stage, symptoms of osteoarthritis such as pain and stiffness become noticeable. Over time, the small cracks and damaged areas deteriorate into larger fissures and irregularities in the cartilage. Holes and pitting in the surface of the cartilage may form lesions that extend right to the bone. As the cartilage wears down, and bone spurs (calluses) may form along the joint margins.

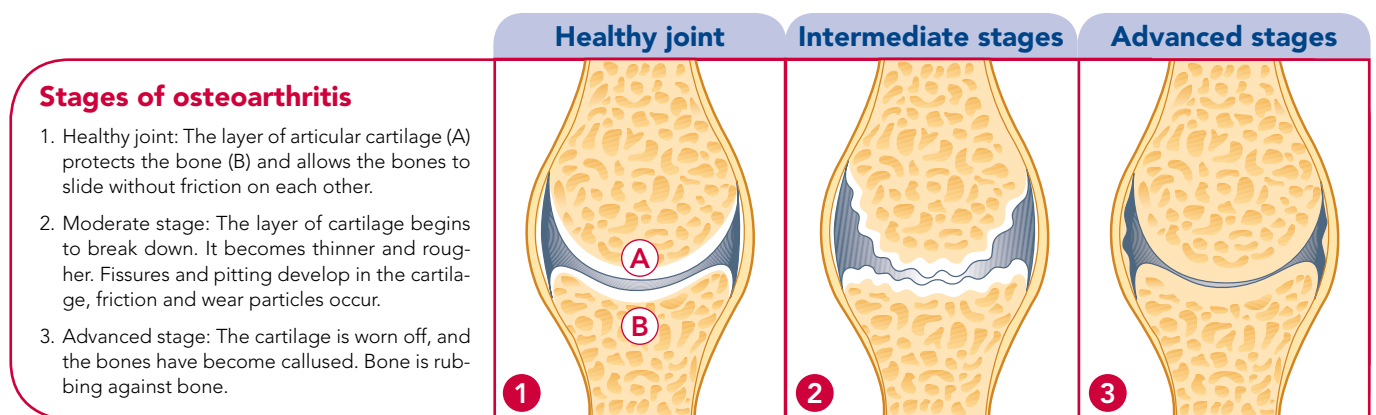
Pain may become worse as the day goes on.

## Late stage

In the advanced stage of joint disease, cartilage has worn away from the bone surface or disappeared completely. The ends of the bone are exposed and rub against the opposing bone without cushioning or protection of any kind. Because the bones are touching, the joint space disappears. At this stage there is severe inflammation, and the joint is often so stiff and painful that it is completely immobilized. The only way to restore function at this point is to replace the joint with an artificial one.

## Diagnosis

Thanks to modern imaging procedures such as magnetic resonance imaging (MRI), pathological changes to articular cartilage can be identified in the early stages. Doctors classify the severity of joint disease according to stages I to IV. In an MRI, the stages can be clearly discerned. This is important because the type of treatment will depend on the severity of the disease.



# Pain: your body's alarm signal

Pain and inflammation are the most important signals that damage is being done to our bodies. The more cartilage cells are destroyed, the greater the pain and inflammation. These signals cause the body to recruit all of its available resources to repair and eliminate the damage as quickly as possible. However, if the body's defense system – the immune system – cannot repair the damage on its own, disease sets in.

## Treating symptoms is not enough

If the pain continues and gets worse, we try to avoid it by favoring the affected joint, adopting a pain-relieving position or avoiding movement altogether. While this is a normal response, it further exacerbates the problem. Because we want to avoid pain, we no longer move the joint normally.

This leads to muscle strain, shortening or atrophy of muscles, and shrinking of the joint capsule. Lack of movement results in a reduced supply of nutrients to the joint, and the ligaments that support and stabilize the knee become weaker.

Drugs are often used to treat the pain, but the use of analgesics is often not enough to disrupt this cycle of cartilage damage, pain, reduced mobility and more damage: once the pain is reduced, the patient will tend to once again put stress on the damaged joint, thereby unknowingly causing more damage.

In this situation the body needs allies – helpers that can tackle the underlying cause of the problem.

# Molecular orthopedics

Molecular orthopedics seeks to understand the biological causes of musculoskeletal disorders, and to develop treatments that intervene in and modify the actual disease-causing factors. This field builds on the knowledge of many disciplines, including orthopedics, molecular biology and physiology. Molecular orthopedics has identified a number of important factors that contribute to osteoarthritis, thus leading the way to the development of treatments for this hitherto incurable disease.

For example, scientists have discovered that the protein interleukin-1 (IL-1), a type of pro-inflammatory cytokine, is one of the main culprits in osteoarthritis.

As one of the components of our immune system, IL-1 has the ability to modify the functions of other cells. This can be positive, as for example when

it enables the body's "repair troops" to quickly reach an area where damage has occurred. However, IL-1 also triggers inflammation and pain inside the joint. These negative effects are one of the main causes behind the destruction of cartilage in osteoarthritis. Identifying the cause of a problem, however, is not enough to be able to eliminate it.

In the late 1980s, a group of researchers in the United States discovered a protein that drives away the pro-inflammatory interleukin-1; they named it interleukin-1 receptor antagonist (IL-1Ra).

Thus, pro-inflammatory IL-1 is a "bad protein," and IL-1Ra is a "good protein" that fights off IL-1 and prevents it from causing inflammation and damage to cartilage.

## “Bad proteins” destroy cartilage

All reactions in our bodies are biochemical processes that share one overriding goal: to maintain a balance in order to ensure the health of the organism. Today, modern technologies give us the tools to identify the mechanisms involved in the causes and effects of disease. In the case of osteoarthritis, the mechanism can be traced primarily to a single, naturally occurring “bad-guy protein” that causes breakdown of cartilage, inflammation and pain: interleukin-1.

But we also have a natural “good-guy protein” that comes to the rescue by blocking the negative effects of interleukin-1. For the sake of simplicity, we will refer to this good protein, which goes by the scientific name interleukin-1 receptor antagonist, as the “anti-arthritis protein.” A number of other “good proteins” and growth factors that

are active in fighting osteoarthritis have also been identified.

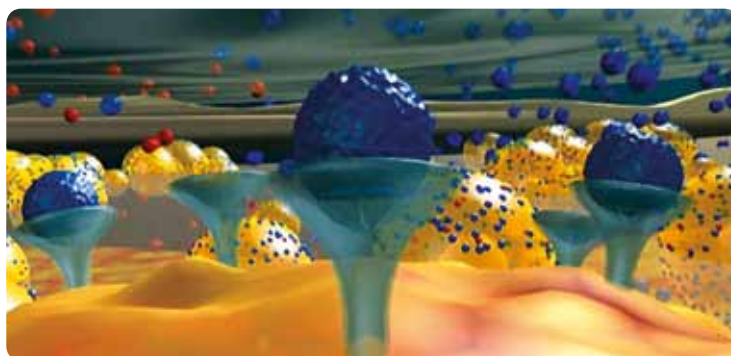
In people with healthy joints, the “good” and “bad” proteins are present in roughly equal numbers, so that a natural equilibrium is maintained. People with osteoarthritis, on the other hand, have too many destructive “bad” proteins and too few of the “good” proteins that fight them off. As a result, the body can no longer defend itself from the overwhelming forces of inflammation or stop the process of cartilage deterioration.

## “Good proteins” protect cartilage

The team of Düsseldorf-based researchers around orthopedist Peter Wehling and molecular biologist Julio Reinecke put their heads together to find a way of defeating the destructive proteins. What would happen, they wondered, if the level of anti-arthritis proteins could be increased to the point that there would be enough “good proteins” in the joint to neutralize the powerful, pro-inflammatory attackers? In order to overcome this enemy on the battlefield, the concentration of natural interleukin-1 antagonists would need to be increased many times.

The scientists wanted to exploit the natural healing mechanisms of the human body in order to be able to intervene at a more fundamental level in the osteoarthritis disease process. For the first time, proteins naturally produced by the body itself – “endogenous proteins” – would be used to treat osteoarthritis. Their research showed that

the “anti-arthritis proteins” were produced by certain blood cells, more specifically by a variety of immune cells from the family of white blood cells. Since the articular cartilage has no blood vessels, the inhibitory substance produced by the blood cells could not be carried to the cartilage by the blood system, but would have to be administered locally to the joint.



# Treatments for osteoarthritis

The early and moderate stages of osteoarthritis are generally treated non-surgically. In the later stages, surgery may be recommended.

## Medications

The purpose of drug therapy is to treat pain and improve joint functioning. A range of pain medications from mild to strong are available. Non-steroidal anti-rheumatic drugs are frequently used since they relieve pain and also reduce inflammation. Many of these pain relievers bring about rapid pain improvement in the short term, but in the longer term they have side effects, and they do not act on the underlying causes of the disease. Glucosamine is also sometimes recommended to support cartilage metabolism. This drug is said to delay the symptoms of osteoarthritis and to slow the breakdown of cartilage.

## Injections

Injections of cortisone, hyaluronic acid or proteins are often used to treat osteoarthritis. The advantage of these treatments is that the active ingredient is administered at high concentrations directly to the joint where it is needed. Intraarticular injections are routine orthopedic treatments that, when performed according to accepted medical practice, are well tolerated.

## Cortisone

Injections of corticosteroid medication may be recommended in inflammatory osteoarthritis, since corticosteroids have a strong anti-inflammatory and analgesic effect. Swelling is generally reduced significantly. However, too frequent corticosteroid injections can further damage joint cartilage, so the beneficial effects must be weighed against the potential side effects.

## Hyaluronic acid

Hyaluronic acid (HA) is naturally present in joint fluid. It helps the parts of the joint to slide freely. The idea of injecting hyaluronic acid directly into the joints of patients with osteoarthritis is that it will "lubricate" the worn joint, allowing the bones to move more smoothly and with less pain. Scientific debate is open whether HA is superior to placebo.

## Non-drug therapies

The aim of non-drug therapies is to stabilize the joint, strengthen the surrounding muscles and improve joint functioning. Physical therapy can be particularly beneficial in helping to improve flexibility and mobility and reduce pain. Acupuncture is another treatment modality that may be particularly effective in reducing the pain of osteoarthritis. Other methods that may be beneficial are water exercise, hot and cold packs, electrostimulation and hydrotherapy.

## Surgery

In moderate arthritis, arthroscopic joint surgery is used, with varying success, to smooth the surface of the cartilage and remove cartilage fragments from the joint. In advanced cases of osteoarthritis, joint pain can only be alleviated by eliminating the mechanical source of the problem. When osteoarthritis has become very severe, joint replacement, especially of hips and knees, is often successful.

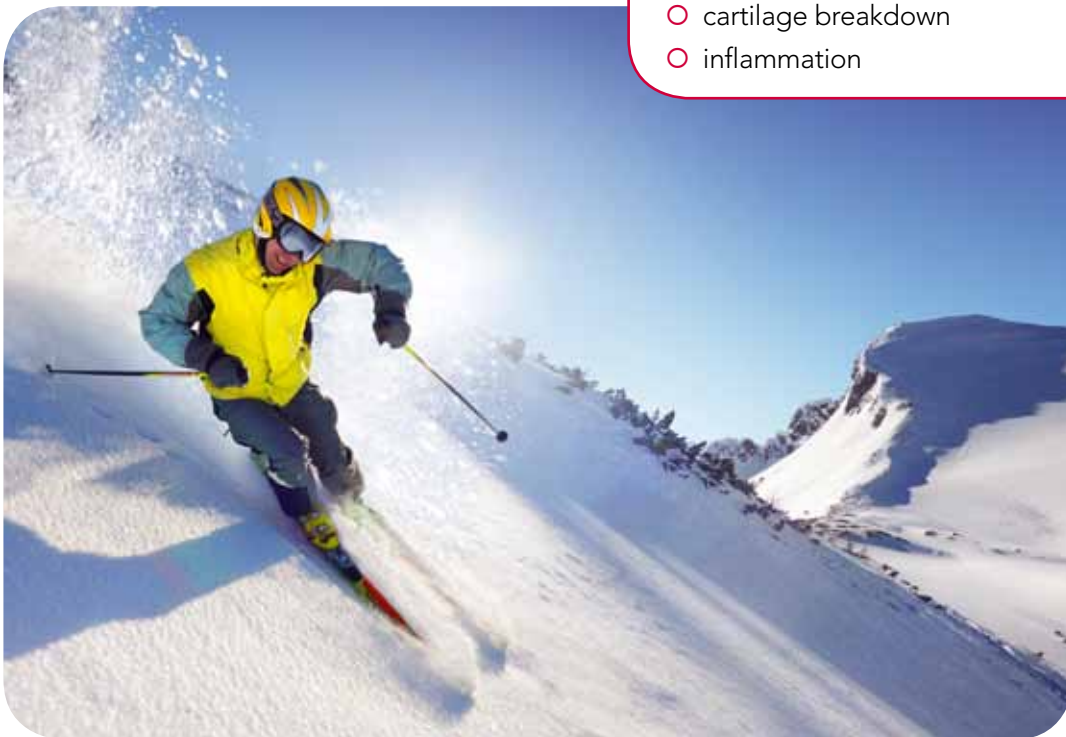
# Orthokine®-therapy

Orthokine®-therapy consists of obtaining “anti-arthritis proteins” and growth factors from the patient’s own blood, and then injecting these endogenous substances back into the affected joint. In order to do so, the physician first collects blood from a vein in the patient’s arm using a special syringe. The syringe containing the blood is stored for several hours in an insulated container at body temperature (incubation). During this time, the blood cells in the syringe are encouraged, by a complex mechanism, to produce high levels of the “good” proteins. After this, the sample is centrifuged to separate solid components of the blood from the serum. The serum contains elevated concentrations of the patient’s own – or endogenous – “good” proteins, which are beneficial for osteoarthritis treatment. Finally, the serum is filled into syringes and subsequently administered directly to the affected joint by injection.

In this way, the imbalance of “good” and “bad” proteins is corrected. Orthokine®-therapy provides a means of increasing the level of “good proteins” directly in the joint, where they can successfully fend off the destructive, pro-inflammatory proteins. The “anti-arthritis proteins” attach to very specific sites (receptors) on the cartilage and synovial membrane cells, thereby preventing the damaging, pro-inflammatory proteins from attacking these cells. Because they are administered directly to the joint, the protective proteins act where they are needed to prevent further cartilage breakdown, inflammation and pain. This method harnesses the body’s own natural medicine to treat osteoarthritis.

## Endogenous proteins – your allies in treating

- joint pain
- cartilage breakdown
- inflammation



# When is Orthokine®-therapy indicated?

Side effects are remarkably rare in Orthokine®-therapy. It can be used for osteoarthritis of the following joints:

- knees
- hips
- ankles
- toes
- shoulders
- elbows
- hands and fingers
- spine

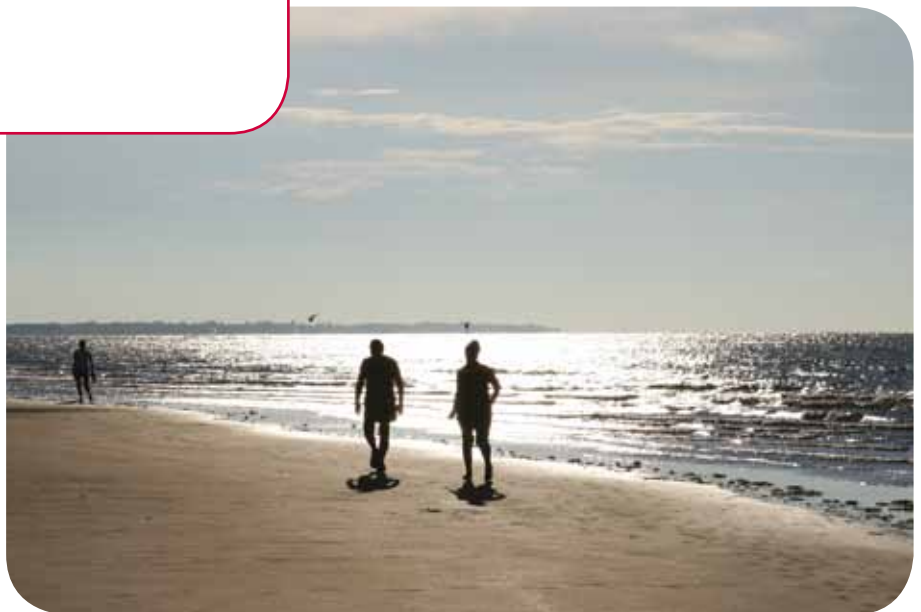
## Orthokine®-therapy is indicated for

- knee joints
- hip joints
- ankle joints
- toe joints
- shoulder joints
- elbow joints
- hand and finger joints
- vertebral joints of the spine

Orthokine®-therapy has also proven very successful in the treatment of prolapsed discs and sciatica. It has been used successfully for inflammations of tendons and ligaments too (e.g. Achilles tendon, Patella tendon, tennis elbow).

This biological therapy makes the body's own healing proteins available for the effective treatment of early to moderate osteoarthritis by inhibiting further cartilage damage in the joint. The natural healing mechanisms of the human body are harnessed to intervene against the underlying causes of disease, with the goal of protecting the remaining cartilage cells against further damage.

Even briefer treatment success can delay the need for joint replacement for a considerable length of time or avoid it altogether. Endogenous proteins are strong allies in the fight against osteoarthritis and in the quest to improve the quality of life of those struggling with this disease.





# What can you expect as a patient?

Orthokine®-therapy supports the body's natural healing mechanism by supplying increased levels of anti-arthritis proteins directly to joints affected by osteoarthritis. Patients usually receive a series of six injections into the affected joint, usually over 3 weeks.

Results are generally apparent within a maximum of six weeks. Pain, inflammation and swelling are noticeably reduced, and mobility of the affected joint improves. Some patients notice improvement after the first few injections.

How long the benefits of the treatment last depends on the severity of the disease and the patient's overall condition. The improvement in symptoms can normally be expected to last anywhere from six months to as much as two years or even longer. Why treatment effects do not last equally long in all patients is not known. It may have to do with the nature of the disease, which varies from one individual to another. It is conceivable that the strength of the defending army of "good proteins" may simply vary from one person to another, and also that, with time, the body's regenerative, healing forces may simply become exhausted.

As the beneficial effects of the endogenous proteins weaken with time, the old symptoms may reappear. In this case the physician may administer further injections. Orthokine®-therapy is not only very effective, but is also very well tolerated, be-

cause it uses substances originating from the patient's own body. The body reacts to the serum in a very natural way, because the serum contains no foreign substances. The proteins are familiar and the body accepts them.

For this reason, no serious side effects specific for Orthokine®-therapy have been observed.

Orthokine®-therapy is recommended for treatment of osteoarthritis in the early and moderate stages, when joint cartilage is only damaged moderately. This method is not recommended when cartilage loss is already very advanced. When bone is rubbing on bone, joint replacement is usually the treatment of choice.

This is why it is very important to seek help at the first warning signs of osteoarthritis. The sooner the process of cartilage breakdown in the joint can be slowed or stopped, the better the prognosis. As long as healthy cartilage cells are still present, the endogenous "anti-arthritis proteins" can exert their natural healing function and work to prevent cartilage damage, inflammation and pain.

