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Information for
healthcare professionals

Dietary management of osteoarthritis: chondroprotectives and micronutrients

Contents

Osteoarthritis: the disease

Definition, pathogenesis and stages of osteoarthritis

Osteoarthritis is the primarily non-inflammatory, degenerative alteration of the cartilage and bone structure in one or more joints, with increasing joint deformation and destruction.

In principle, all joints of the body may be affected. The most common forms, however, are osteoarthritis of the knee and hip, the shoulder, the small finger joints, or the spine. Osteoarthritis is subdivided into a primary and a secondary form, with different characteristics for knee and hip osteoarthritis (Table 1).

Pathological alterations are mostly caused by congenital cartilage defects, injuries or unphysiological loads on the joint. They result in pain and stiffness of the affected joint as well as progressing deformation. In the final stage of the disease, the joint may be totally ossified. This process can be retarded by various interventions, but in the advanced stage of the disease only surgical joint replacement (arthroplasty) can be considered as the ultimate treatment option.

An imbalance between the load exerted on the joint cartilage and its load bearing capacity will lead to the degradation of cartilage tissue. For example, a false valgus position of the knee joints or a slightly false congenital hip position can result in an unbalanced load and thus in osteoarthritis of the corresponding joints. Cartilage damage due to accidents or joint surgery long ago can cause also osteoarthritis. Excess body weight places intense strain on the supporting joints, such as the knee and hip joints.

Thus, for instance, in manifest obesity two or three times the normal body weight presses on the cartilage.[39] General risk factors are old age, female gender and an inherited predisposition.

Joint alterations in detail. The diseased cartilage is worn away until eventually in the final stage the bone is reached. To some extent as a supporting reaction, bone is grown around the affected joint and forms bony spurs at the periphery, called 'osteophytes', leading to deformation and knotty swellings of the affected joints. Abraded cartilage and bone material in the synovial fluid causes inflammation of the surrounding synovial membrane ('detritus synovitis') and, as a result, recurrent overheating and reddening of the joints. In addition, a joint effusion may develop. This is the stage of activated osteoarthritis (see page 8, stages of osteoarthritis).

Table 1. Primary and secondary causes of hip and knee osteoarthritis[33]

	Hip osteoarthritis	Knee osteoarthritis
Primary	- Clinical manifestation usually after 50 to 60 years of age - Predominantly bilateral occurrence	Clinical manifestations - In adolescents: femoropatellar - More frequently in women - In adults: femorotibial more frequently from 40 on - Additional increase in post-menopausal women
Secondary (causes in the order of frequency)	- Congenital hip dysplasia/hip luxation - Epiphysiolysis of the femoral head - Necrosis of the femoral head, primary and secondary - Protrusio acetabuli - Rheumatoid arthritis - Bacterial infection of the hip - and others	- Axial deviations - Injuries of the knee joint - Arthropathies (metabolic, neuro-genic, endocrine, with hemophilia, with systemic diseases) - Rheumatoid arthritis - Bacterial arthritis - and others

The synovial membrane, chondrocytes, macrophages and T cells are involved in the development of joint inflammation. Moreover, the cytokines in the extracellular matrix and prostaglandins play an important role. Cytokines and free radicals, which may also accumulate during an inflammation, can diffuse freely into the cartilage and impair the proteoglycan and collagen synthesis of the chondrocytes.[138] Besides an increased number of metalloproteinases, such as stromelysin and collagenases, are produced and promote cartilage degradation.[44]

Cartilage degradation products occasionally adopt a behavior similar to antigens. If they reach the synovial fluid due to excessive catabolism, synovitis, i.e. an inflammation of the joint inner lining, will be induced. This inflammation can affect the metabolism of the local synoviocytes. The cells essentially produce hyaluronan. However, as a consequence of the inflammatory process, more plasma enters the joint fluid, which decreases the hyaluronan concentration. The dilution of the joint fluid as well as the reduction in molecular weight results in decreased viscoelasticity. The joint fluid thus loses its specific lubrication and protection characteristics.[138]

The following stages of osteoarthritis are differentiated:

I. Pre-osteoarthritis
Joint incongruency with the consequences of unphysiological load; damage of the cartilage surface not yet present; no symptoms

II. Silent or clinically latent osteoarthritis with a targeted examination, clinical and X-ray signs may be found

III. Activated osteoarthritis
Damage to the cartilage surfaces, cartilage fractures, which however do not reach the underlying bone; severe symptoms due to capsule inflammation induced by overloading the joint that is already osteoarthritic, or the impact of 'irritating factors', such as excess body weight, persisting static false posture, mechanical strain due to work and sports, endogenous metabolic disturbances, or traumatic lesions

IV. Decompensated osteoarthritis
Cartilage destruction with exposed bone, serious joint damage, also extensive defective areas with wastage of large parts of the joint surface; permanent pain

Symptoms of osteoarthritis

Pain is the predominant symptom of osteoarthritis with about half of the patients affected only suffering from pain episodes that occur approx. 1-2 times per month. But in many patients the pain may last for longer than 6 months. In the early stages of the disease start-up/fatigue pain and pain upon pressure is perceived, whereas in the late stages the pain is permanent. The great discrepancy between the radiologic alterations in the joint and the complaints of the patients is striking: as data from the Netherlands show, physician and patient only agree on the evaluation of the complaints in about 10% of the cases.[96]

Besides pain, functional restrictions and restricted mobility are the symptoms that cause problems in everyday life, such as walking up stairs, or going shopping. Normal joint function is crucial to maintaining walking speed, quality of life and social activities.

Prevalence and incidence

The risk of developing osteoarthritis increases with age. Whereas only 4% of 20-year-olds have osteoarthritis, 70% of the population aged over 70 is affected. Women are more at risk than men. In the elderly, osteoarthritis is the most frequent joint disease, but it is not a consequence of natural aging processes.

Every year the number of people with osteoarthritis grows by around 2%, and in about half the new cases the diagnosis is connected with symptoms. The condition progresses in 4% of the patients every year.[96]

We know from postmortal skeleton studies that the frequency of osteoarthritis in recent years – compared with past decades or centuries – has clearly increased. As there are no data available from Germany, the German Federal Ministry of Health is currently using data from the Netherlands according to which 35 million people in Germany have radiologically detectable osteoarthritis, of which between 5 and 15 million have manifest symptoms. (Federal Health Monitoring System, quoted in Schneider et al.[109]).

Relevance to the healthcare system

There is no doubt that osteoarthritis must be treated, as for many patients this is the only chance of being active outside their home without having to rely on external help.

The direct cost of the diagnosis and treatment of osteoarthritis is estimated to total approx. € 5 billion in Germany every year. This does not include indirect costs such as those caused, for example, by the loss of working hours, and not least the impairment of the quality of life ('intangible costs').

Thus, the costs incurred by diseases of the musculoskeletal system are much higher than for cardiovascular diseases. As a result of the NSAID medication (non-steroidal anti-inflammatory drugs) often used to treat osteoarthritis, gastrointestinal diseases may be caused or aggravated. The average cost of their treatment will be doubled if NSAIDs are taken, as NSAIDs drastically increase the risk of hospitalization, ulcers, ulcer bleeding or fatal ulcer bleeding. Especially in older patients, NSAIDs are the most frequent cause of adverse drug reactions.[96]

Diagnosis and therapy

In addition to a detailed case history and physical examination, X-ray images of the affected joints (Fig. 1) are very important for diagnosis.

Secondary severe axial malposition (varus) due to degenerative processes

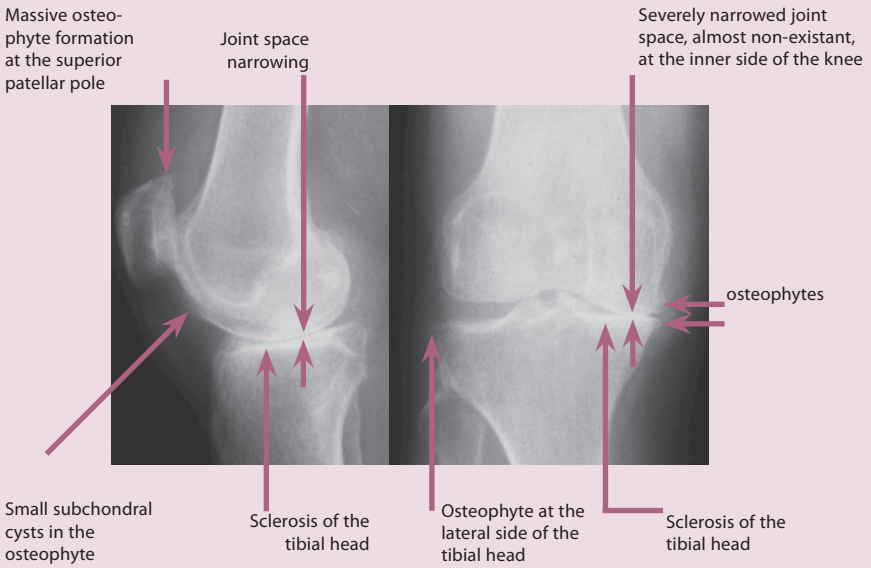


Fig. 1. Osteoarthritic knee joint in X-ray images

Certain osteoarthritic alternations are identified, such as narrowing of the joint cavity, osteophyte formation, sclerosis (densification) of the adjacent bone, and possibly deformation.[65]
In order to evaluate the clinical picture and control therapy, validated questionnaires and/or analog scales are now used on a more frequent basis.

Table 2. Test instruments: VAS, Lequesne and WOMAC indexes

Visual analog scale: pain
Assessment scale of 10 cm length, where patients indicate their subjective pain intensity; 0 = no pain, 10 = worst pain imaginable (a range of 0 to 100 mm is commonly used in studies)

Lequesne index
Knee or hip questionnaire, questions on: A. Pain or discomfort (5 questions) B. Maximum distance walked (1 question) C. Difficulties encountered while performing everyday tasks (6 questions)

WOMAC* index
Validated questionnaire with the following subscales: A. Questions on pain (5 questions) B. Questions on joint stiffness (2 questions) C. Questions on physical activities (17 questions)

* Western Ontario and McMaster Universities Osteoarthritis Index

The therapy of osteoarthritis has so far focused more on the symptoms of the disease and less on its causes: analgesics, NSAIDs and steroids are still the main pillars of treatment. In recent years other interesting concepts of complementary medicine have also been developed. Numerous studies have thus been published that investigate the influence of nutrition on osteoarthritis. In this context, it is mainly the substances that protect the cartilage (chondroprotective substances or, more precisely, SADOA*) and certain micronutrients (vitamins, minerals, trace elements, amino acids, essential fatty acids, and phytochemicals/phytonutrients) which play a crucial role.

In this brochure the focus is on SADOA, also called slow acting drugs on osteoarthritis, and micronutrients and their special nutritive importance to dietary management of osteoarthritis.

* SADOA = slow-acting drugs in osteoarthritis

SADOA and related substances

The following sections will provide an overview of the literature available on SADOA and explain the nutritional features and characteristics of these substances for joint metabolism. These interesting chondroprotective substances primarily include glucosamine sulphate and chondroitin sulphate, but also collagen hydrolysate. They have synergistic effects.

Glucosamine sulphate

Basic facts. Glucosamine (more precisely 2-amino-2-desoxy-D-glucose) is an amino monosaccharide that is produced by the body in the glucose metabolism. It belongs to the group of mucopolysaccharides and is used, for example, for the build-up of glycolipids, glycosaminoglycans, hyaluronic acid and proteoglycans. Glucosamine is mainly needed for the synthesis of chondroitin sulphate and hyaluronic acid which represent the scaffold for collagen formation.

Glucosamine is obtained from chitin, a polymer that is present in the exoskeletons of crustaceans (crabs, lobsters) and in mushroom cell walls. A frequent glucosamine compound is glucosamine sulphate (GS). It plays an important role in the cartilage metabolism because it is a natural component of the most important glycosaminoglycans (GAG) that are present in the synovial fluid and the cartilage matrix.

Preclinical studies on absorption. Studies with rats and dogs have shown that radioactively labeled glucosamine taken orally is readily absorbed by all tissues, including the cartilage.[115,116] In human studies 90% of the glucosamine taken orally was absorbed (Setnikar and Rovati[114] quoted in Anderson et al.,[4] Setnikar et al.[117]).

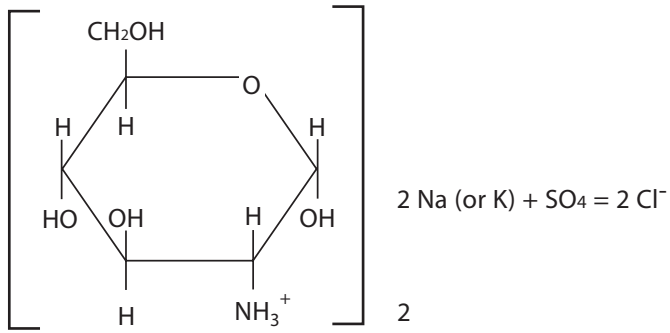


Fig. 2. Chemical structure of glucosamine sulphate

Support for the cartilage metabolism and suppression of inflammation. Animal models using chondrocyte cultures from cartilage with osteoarthritic alterations showed that GS increases the proteoglycan synthesis.[137] Noyszewski et al. (2003)[87] demonstrated that glucosamine is preferentially incorporated in the cartilage. The addition of glucosamine sulphate to the culture medium stimulated the cartilage cells, dependent on the dosage, to synthesize rising amounts of proteoglycans, such as aggrecan.[35] Another study showed that GS leads to a doubling of the gene expression of the most important cartilage proteoglycans, i.e. aggrecan and perlecan.[61]

In addition, anticatabolic properties could be detected. Thus, in the cartilage cells of osteoarthritic patients glucosamine inhibited collagenase (key enzyme in osteoarthritic cartilage destruction) and its activator, i.e. cellular phospholipase A_2. This inhibits collagenase activity.[98] It was shown in gene expression analyses that glucosamine sulphate causes a moderate but constant reduction in stromelysin mRNA.[61] Moreover, dependent on the dosage, glucosamine decreases the production and activity of the matrix metalloproteinases (MMP) 1 and 3 in the chondrocytes of knee joints with osteoarthritic alterations[34,35] and the aggrecanase in bovine cartilage samples.[106]

Structure-modifying effect. The administration of GS supports the cartilage metabolism by dietary management, as exogenous sulphate plays a major part in glycosaminoglycan synthesis. This characteristic could also be important in connection with the damaging effect of NSAIDs on the cartilage. Thus, in animal experiments paracetamol reduced the concentration of inorganic sulphate in the blood.[132] Several animal models confirmed that NSAID intake leads to a reduction in the GAG synthesis of the cartilage.[132,137]

Several studies with rabbits and dogs dealt with the influence of GS on cartilage destruction during the development phase of osteoarthritis. It was found that cartilage destruction was significantly reduced with GS administration.[22,88,94] Based on these animal models, it could thus be proved that GS actually has structure-modifying properties.

The anti-inflammatory properties of glucosamine were demonstrated in several in-vitro studies[19,70,120] and animal models.[113,114] GS, as it was shown, inhibits in rats the proinflammatory effects of various substances, such as carrageen or formalin. In an animal experiment, glucosamine sulphate could also inhibit lysosomal enzymes and the formation of superoxide radicals with macrophages.[113] On the basis of the therapeutic index, glucosamine sulphate was 10 to 30 times more efficient than indometacin.[113]

The protein synthesis of cyclooxygenase-2 (the key enzyme for prostaglandin conversion) is also inhibited by glucosamine.[70] Chan et al.[19] and Shikhman et al.[120] demonstrated on bovine cartilage explants that glucosamine and chondroitin reduce the expression of genes that are involved in nitric oxide (NO) and prostaglandin-E_2 (PGE_2) synthesis and in this way reduce the inflammatory mediators NO and PGE_2.

Table 3 provides an overview of the nutritive characteristics of GS. In contrast to the frequently administered unspecific drugs with a symptomatic effect (e.g. NSAIDs), GS leads to a symptomatic and structural modification by means of dietary management.

Clinical studies. In three clinical studies performed between 1980 and 1994[36,86,124] (quoted in Ulbricht et al.[131]), a total of 1,540 osteoarthritic patients took GS for a period of 4 to 8 weeks (3 x 500 mg daily). As a result of this treatment, the patients reported a significant reduction in pain, less sensitivity to pressure, less swelling of the joints and greater joint mobility as compared with the placebo.
The physicians also evaluated the improvement as very good or good in a higher percentage of the patients in the GS group vs the placebo group. In the open non-controlled study of Tapadinhas[124] the physicians stated a good improvement in 58.7% and an adequate improvement in 36% of the patients. The improvement was only found to be inadequate in 5.3% of the patients.

Comparison with NSAIDs. Currently there are 10 studies comparing glucosamine and NSAIDs. Vaz[133], Müller-Fassbender et al.[83], Rovati et al.[104,105], Förster et al.[42], Qiu et al.[99] and Thie et al.[125] studied the effect of orally administered glucosamine or NSAIDs on knee joint and/or temporomandibular joint osteoarthritis. Thie et al.[125], D'Ambrosio[29], Mund-Hoym[84] and Crolle[25] gave osteoarthritis patients glucosamine not only orally but also as intramuscular, intra-articular or intravenous injections.

In comparison with NSAID application, glucosamine led to a comparable reduction in the clinical parameters of pain scale, Lequesne index, etc. in the studies. Müller-Fassbender[83] and Qiu[99] documented that glucosamine was significantly better tolerated by the patients than NSAIDs.

Structure-modifying effect of glucosamine sulphate (GS)

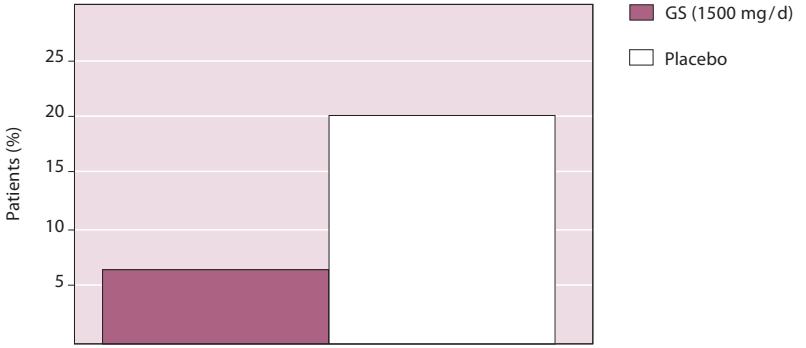


Fig. 3. Number of patients showing joint space narrowing of ≥ 0.5 mm at the end of a 3-year trial (p = 0.0007); modified after Bruyere et al. 2004[16]

Symptom-modifying effect of glucosamine sulphate (GS)

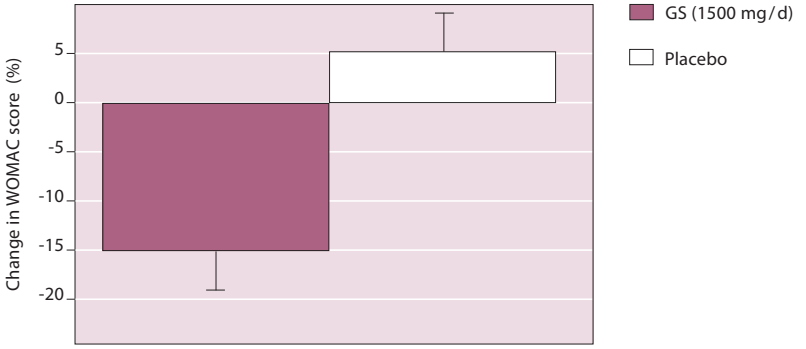


Fig. 4. Mean change in WOMAC score after three years (p = 0.003); modified after Bruyere et al. 2004[16]

Table 3. Nutritional features and characteristics of glucosamine sulphate

Glucosamine sulphate
Support of cartilage metabolism
Necessary component of cartilage cells for synthesis of glycosaminoglycans and proteoglycans[87,137]
Stimulates cultured human cartilage cells to form proteoglycans[6]
Anti-inflammatory
Inhibits the effect of superoxide radicals, lysosomal enzymes[113]
Inhibits the synthesis of inducible nitric oxide[120]
Inhibits the synthesis of prostaglandins[19]
Beneficial effect on symptoms
Relieves joint pain in osteoarthritis patients[131]
In comparative trials with NSAIDs, to some extent better effect with regard to pain reduction[25,29,42,84,99,133]

Chondroitin sulphate

Basic facts. Chondroitin sulphate (CS) is an important component of most tissues and is mainly present in the extracellular matrix (ECM). It is therefore found in the body's connective tissues, such as cartilage, skin, blood vessels, and also in bones, ligaments and tendons. In collagen fibers that are oriented predominantly in one dimension, e.g. ligaments and tendons, the GS content is rather low, but in other tissues without a predominant collagen fiber orientation, e.g. the skin, it is very high. This gives the tissue the ability to expand under strain but also makes it very firm and resistant to compression at the same time.

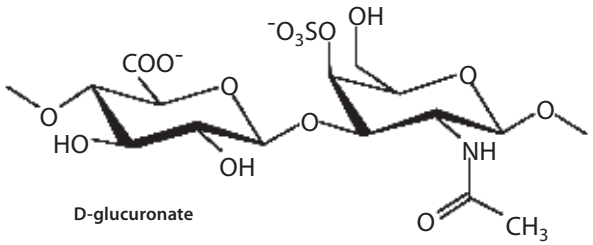


Fig. 5. Chemical structure of chondroitin 4-sulphate

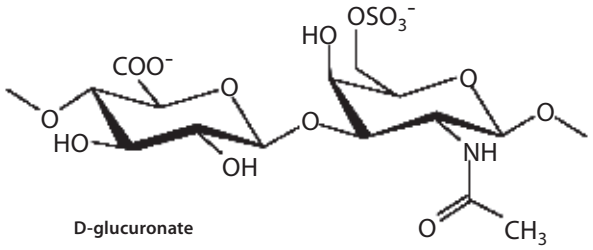


Fig. 6. Chemical structure of chondroitin 6-sulphate

CS is a **branchless, complex glycosaminoglycan** that can be extracted from various tissues (for instance from shark cartilage, bovine tracheal cartilage). It is a polyanion with some of its properties being generated by the heavy load. It can draw **water in the tissue** and hydrate it. CS consists of repetitive non-sulphated or sulphated **disaccharide units** (N-acetylgalactosamine + glucuronic acid; Figs. 5 and 6).
CS chains have a covalent bond with proteins and are released to the ECM as proteoglycans (Fig. 7). Some **proteoglycan** families containing CS chains have now been identified, with the aggrecan family being the most important one. Members of the **aggrecan** family are characterized by a very high molecular weight of > 500 kDa and extracellular aggregation by binding to hyaluronan (a proteoglycan).

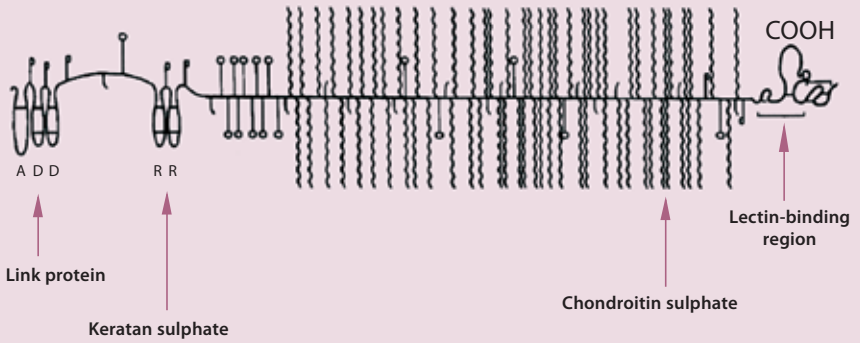


Fig. 7. Schematic drawing of the aggrecan structure, showing core protein and polysaccharides[138]

Joint cartilage is a **highly specialized tissue with a strongly expanding ECM**. It consists of 98% matrix and < 2% cells. The individual distribution of its components, i.e. the fiber collagen and the non-fibrous proteoglycans, determine its properties. By filling up the interfibrillar matrix with a large amount of proteoglycans that are rich in GS, in particular aggrecan, the **cartilage is made resistant to compression**. As aggrecan in high concentration attracts water, the tissue will swell and expand and put the collagen network under strain. As a result of the **equilibrium inside the hydrated tissue**, the cartilage reaches a high level of resilience.

CS has a broad range of functions, mainly as a result of the many strongly sulphated sections of its structure which can interact specifically with other molecules. At sites of inflammation, proteoglycans are released either by activated mononuclear leucocytes or as a result of ECM degradation. Chondroitin-4 sulphate proteoglycans are mainly produced by activated human monocytes/macrophages. It is able to activate monocytes for the secretion of monokines and induce the proliferation of B cells.

Important in-vitro and in-vivo results. In various in-vitro studies or animal experiments the oral intake of CS with the diet caused

- a significant reduction in the formation of granuloma, e.g. after implantation of cotton or sponge particles,
- an inhibition of the inflammatory response in arthritic patients, and
- an inhibition of the release of lysosomal enzymes in experimentally induced pleuritis.[138]

Moreover, CS also inhibits the directional chemotaxis in specifically activated serum. It lowers the rate of phagocytosis and the lysozyme release and protects the cell membranes against reactive oxygen species.[138]

In an in-vitro study[7] the observation was made that the addition of CS to a culture medium led to an increase in the proteoglycan concentration in the extracellular matrix. Moreover, it caused a dose-dependent decrease in the collagenolytic activity that was released from human joint cartilage cells in the culture.

When the effect of CS on a specially induced joint cartilage lesion was studied in a rabbit model, it was found that the cartilage of the animals that had previously been given intramuscular or oral CS lost less proteoglycan than the cartilage of the control animals.[129]

Clinical studies. In the period between 1992 and 1998, a number of very informative studies on special dietary foods with the supplementation of chondroitin sulphate were published:

- In all, 120 patients with knee joint osteoarthritis were treated with CS vs a placebo. Based on a visual analog scale (VAS), a significant reduction in the joint pain and the Lequesne score was observed. Moreover, the CS treatment was evaluated more favorably by patients and physicians. The 3-month treatment phase was followed by a 2-month phase without treatment to identify the longer-term effects and especially the need for NSAIDs (in mg diclofenac equivalent).
  After the 3-month treatment, the patients needed significantly fewer NSAIDs. This effect lasted for another 2 months. No patient dropped out of the study prematurely, and no tolerance to the active agent developed.
  According to the results, CS is a useful dietary therapy for osteoarthritis which was demonstrated by both the 'slow' improvement in osteoarthritis symptoms (SYSADOA*) and by the reduction in NSAID consumption.[75]
- Of 146 patients with knee joint osteoarthritis, 74 received 3 x 400 mg of CS daily for 3 months, then the therapy was discontinued for 3 months. A control group of 72 patients received 3 x 50 mg of diclofenac daily for 1 month, then no therapy for 5 months. The patients treated with diclofenac had less pain in the knee joint after 10 days, an effect that disappeared when the therapy was discontinued. The patients treated with CS responded to the therapy significantly after 30 days, and this result lasted for more than 3 months after discontinuation. The Lequesne score of the patients that had taken CS dropped by 87% after 3 months, after 1 month of diclofenac it dropped by 63%. Three months after discontinuation of CS the Lequesne score was still 64.4% lower than it had been when the study was started. Three months after discontinuation of diclofenac this score was only 29.7% lower than at the beginning of the study.[81]
- In another placebo-controlled double-blind trial 56 patients with knee joint osteoarthritis were treated with 800 mg of CS daily for 1 year. The CS group showed significant improvements with regard to mobility and decrease in joint effusion and joint swelling.[40]
- Busci and Poor[17] compared 40 patients suffering from knee joint osteoarthritis who had been given 800 mg of CS daily for 6 months with 40 patients taking a placebo. The CS group demonstrated a significant improvement in the Lequesne and pain VAS scores and in the walking speed over a distance of 20 m. Moreover, the effectiveness of CS was evaluated more favorably by both patients and physicians. The CS group took significantly less paracetamol.

* SYSADOA = symptomatic slow-acting drugs in osteoarthritis

- Patients with knee joint osteoarthritis were treated with either 1 x 1,200 mg of CS gel, 3 x 400 mg of CS capsules taken orally, or a placebo. The Lequesne score and the pain VAS score decreased significantly in both CS groups vs a placebo. CS was also significantly preferred in the overall opinion of patients and physicians. Of the 127 patients overall, 40 patients taking CS gel, 43 taking CS capsules and 44 taking a placebo were evaluated after 3 months. When comparing the administration of CS gel 1 x daily and CS capsules 3 x daily, amounting to the same daily dose in each case, no differences were found in any of the clinical parameters.[14]
- In order to determine the clinical, radiological and biological effectiveness of CS, the medial joint cavity of the knee joint was determined by computer in patients who were treated with 800 mg of CS daily vs a placebo. After 1 year the joint cavity width in the placebo group had significantly narrowed, in the CS group, however, it had remained unchanged. In the controlled, double-blind, pilot study including 42 patients with knee joint osteoarthritis it was confirmed that **CS is well tolerated and reduces the pain significantly and/or increases overall mobility by dietary management**. The CS treatment stabilized the joint cavity width, whereas it narrowed in the placebo patients. Various biochemical markers of the bone and joint metabolism were also improved by CS. Altogether, it could be shown that CS taken orally is an effective and safe SYSADOA, whereby it was proven for the first time that CS is able to **favorably influence the course of osteoarthritis in humans**.[130]
- In another study, the X-ray images of the hands of 119 patients with osteoarthritis of the small finger joints were examined. Thirty-four patients were given 2 x 400 mg of CS daily (85 patients were given placebo). X-rays were made annually for 3 years. In the CS group, the number of patients who had developed new erosive osteoarthritis dropped significantly. The treated patients were thus protected against an erosive development of the disease, which indicates a chondroprotective effect of CS.[135]

Administration of chondroitin sulphate results in significant pain relief

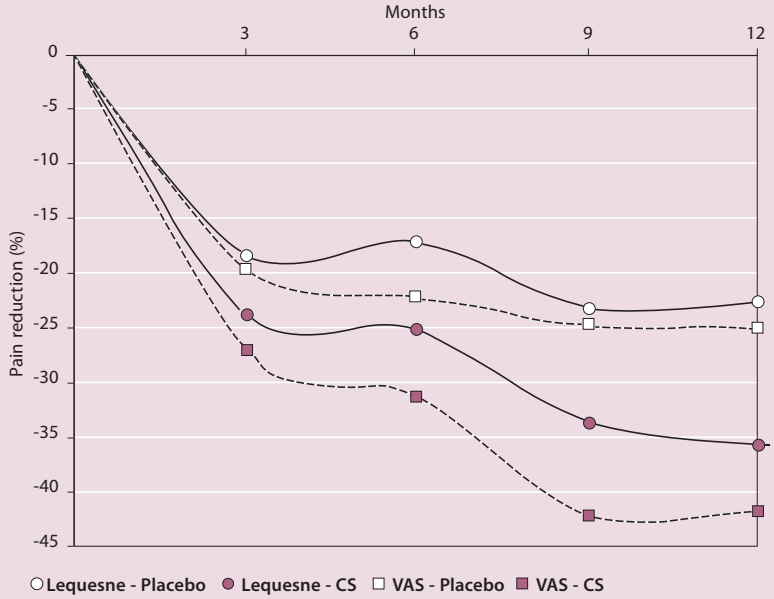


Fig. 8. Procentual change of Lequesne and VAS score; modified after Uebelhart et al.;[128]
* $p < 0.05$, ** $p < 0.01$; CS: 800 mg/d

Table 4. Nutritional features and characteristics of chondroitin sulphate

Chondroitin sulphate
Support of cartilage metabolism
Component of proteoglycans, especially aggrecan[138]
Raises the proteoglycan concentration[7] → Proteoglycans attract water and increase the cartilage's resistance to compression and tension
Anti-inflammatory
Immunomediator with inflammations[138]
Inhibits the release of lysosomal enzymes[138]
Protects the cell membranes against free radicals[138]
Beneficial effect on symptoms
Relieves joint pain in osteoarthritis patients[14,17,130]
When administered simultaneously, fewer NSAIDs are needed[75]

Symptomatic slow acting drugs in osteoarthritis may have synergistic effects when given in combination. Thus, a recent study proved that giving patients with severe pain (baseline value 301-400 mm in the WOMAC pain subscale) a nutritive combination of glucosamine-HCl (3 x 500 mg) and chondroitin sulphate (3 x 400 mg) was significantly more effective than a placebo. As single substances (glucosamine-HCl and/or chondroitin sulphate) and the NSAID used (Celecoxib 200 mg daily) did not show any significant differences compared with the placebo in this patient group.[21]

Table 5. More recent clinical trials with glucosamine, chondroitin and other micronutrients*

Study	Daily dose**	Study design	Pts. (n)	Parameters	Results	Authors' conclusion
Knee osteoarthritis						
Reginster et al. 2001[100]	1 x 1,500 mg GS	randomized, placebo-controlled, prospective, double-blind 3 years	212 pts. 50 M. 163 F. GS: 106 Plc: 106	• X-ray knee joint, under strain • JSW • JSN • WOMAC • AFI	• **Plc:** progressive JSN of -0.31 mm • **GS:** insignificant JSN of -0.06 mm • Improvement in WOMAC scores with GS • Deterioration with Plc • No difference in tolerability	In the long term both structure- and symptom-modifying effects of GS could be shown.
Pavelka et al. 2002[93]	1 x 1,500 mg GS	randomized, placebo-controlled, prospective, double-blind 3 years	202 pts. GS: 101 Plc: 101	• X-ray knee joint, under strain • JSN • AFI • WOMAC	• **Plc:** progressive JSN of -0.19 mm • **GS:** insignificant JSN of -0.04 mm (p=0.001) • Symptom improvement of 20%–25% with GS: significant difference in AFI and WOMAC scores • No difference in tolerability	The long-term therapy with GS reduced the progression of knee osteoarthritis. This shows that GS is potentially able to have an impact on the disease.
Bruyere et al. 2004[16] see Figs. 3 and 4	1 x 1,500 mg GS	randomized, placebo-controlled, prospective, double-blind 3 years	319 postmenopausal women (of a total of 414 pts.) → Total pts. from Reginster 2001 and Pavelka 2002	• X-ray knee joint, under strain • JSW • JSN • WOMAC	• Baseline JSW: 3.8 mm • **GS:** no additional JSN: +0.003 mm **Plc:** -0.33 mm ($p < 0.0001$) • Relevant (> 0.5 mm) JSN: **GS:** 6.9% **Plc:** 20.6% • WOMAC: significant improvement with GS: -14.1%, with Plc: 5.4% (worsened) • Significant improvement in "pain" ($p < 0.02$) and "function" ($p = 0.004$)	The analysis of both long-term studies showed for the first time that the intervention improved symptoms and retarded the structural progression of knee osteoarthritis in postmenopausal women.
Christgau et al. 2004[20]	1 x 1,500 mg GS	randomized, placebo-controlled, prospective, double-blind 3 years	212 pts. 50 M. 162 F. GS: 106 Plc: 106 → Patient group from Reginster 2001	• Markers of cartilage degradation CTX-II (CartiLaps ELISA)	• OA pts. have higher CTX-II levels at baseline: 222.4 ng/mmol vs 169.1 ng/mmol in individuals with healthy joints • Pts. with a high cartilage turnover showed a significant decrease of CTX-II after 1 yr of GS therapy. This correlated with the JSW after 3 years. • Higher CTX-II values correlated with a worse WOMAC result	The assessment of C-telopeptide fragments for urinal type-II collagen identified OA pts. with high cartilage turnover who responded the most to the therapy with structure-modifying substances.
Uebelhart et al. 2004[128] see Fig. 8	800 mg CS	randomized, multi-center, placebo-controlled, double-blind intermittent treatment 2 x 3 months per year	120 pts. ITT: CS: 54 Plc: 56 after 12 months: CS: 43 Plc: 41	1. Lequesne AFI 2. Clinical parameters (incl. pain using VAS) 3. X-ray knee joint, under strain	• **AFI:** after 12 months with CS decrease of 36%, with Plc only 23% • **VAS:** significantly reduced with CS (42% vs 25%) • Walking speed: increased with CS • Assessment by pts. and physicians: significantly in favor of CS: good or very good 89% of pts. vs 13% very good, 36% good in the Plc group • NSAIDs: with Plc significantly higher use of paracetamol vs CS (55.5 tabl. vs 25.8 tabl.)	An improvement in symptoms and a sustained treatment effect was also demonstrated with an intermittant therapy administered two times per year (3 months).

* This table provides an total overview of the current literature on SADOA and related substances; it serves to explain the nutritional features and characteristics of the substances in relation to the joint metabolism.
** Unless otherwise stated, substances were administered orally.

Study	Daily dose**	Study design	Pts. (n)	Parameters	Results	Authors' conclusion
Knee osteoarthritis						
Clegg et al. 2005[21]	Combination: 3 x 500 mg GHCl + 3 x 400 mg CS or each single substance Celecoxib 200 mg (CE)	randomized, multi-center, placebo-controlled, double-blind 24 weeks	1,258 pts. Severity: Kellgren degree 2–3 subgroups: WOMAC pain 301-400 mm or 125-300 mm at baseline	• WOMAC index: response rate of 20% pain reduction • Other WOMAC subscales • HAQ • Acetaminophen use	• Primary endpoint (total group): the CE response rate of 70.1% was significantly higher than with a placebo (60.1%). • With baseline pain score of 301-400 mm: **response rate G+CS of 79.2% significantly higher** than placebo ($p = 0.002$) and **higher than that of G and CS alone, or that of CE alone.** • The other parameters show changes which are consistent with the results of the primary endpoint.	The combination of G + CS proved to be effective for the treatment of moderate to severe osteoarthritis pain of the knee joint. Here the response rate with the combination was higher than with CE or the single substances, and significantly higher than with the placebo.
Das and Hammad 2000[31]	Combination: 2 x 1,000 mg GHCl + 800 mg Na-CS + 152 mg Mn-ascorbate	randomized, placebo-controlled, 6 months	93 pts. Comb.: 46 Plc: 47 (mild to moderate OA in X-ray)	• Lequesne ISK • WOMAC • Pts. assessment	• Significant improvement of ISK after 4 and 6 months ($p = 0.003$ and $p = 0.04$, resp.) • Response rate: 52% comb. vs 28% Plc • Severe OA (n = 21): no significant improvement of ISK • Pts. assessment for the combination: significantly improved • WOMAC: not significant	The combination of GHCl, So-CS and Mn-ascorbate is effective for mild to moderate knee osteoarthritis (according to ISK score).
Qiu et al. 1998[99]	**GS:** 3 x 2 cps. (250 mg) = 1,500 mg **IBU:** 3 x 1 tabl. (400 mg) = 1,200 mg	randomized, controlled, double-blind 4 weeks (+ 2 weeks without therapy	178 pts. GS: 87 pts. IBU: 81 pts.	• Pain when resting, in motion and upon pressure • Swelling of the knee • Treatment outcome • Tolerability	• **GS and IBU** improved the symptoms significantly, however, the trend for GS was stronger • 2 weeks after discontinuation both showed some residual effects. This trend was stronger in the GS group, however. • GS was tolerated significantly better than IBU.	The efficacy of GS was clearly proven, and there was confirmation of the previous results of Müller-Faßbender et al. (1994) which suggest that GS is tolerated significantly better than IBU. In addition, the effect was sustained for a longer time period after discontinuation.
Finger joint osteoarthritis						
Verbruggen et al. 2002[136]	1. CPS 50 mg twice a week for 8 weeks every 4 months	randomized, placebo-controlled, double-blind 3 years	CPS: 66 Plc: 64 after 3 yrs. CPS: 46 Plc: 46	• X-ray DIP, PIP and MCP joints • 2 anatomical rating systems • VAS	Two numerical rating systems: 1. Anatomical Lesion Progression System 2. Anatomical Phase Progression System **Results for IP joints:** • The occurrence of OA could not be prevented; however, the OA progression was less pronounced in the CPS and CS groups vs Plc group. • Fewer pts. in the CS group (8.8%) developed an erosive OA vs Plc pts. (29.4%)	The rating systems used for osteoarthritis of finger joints demonstrate the disease-modifying effect of both chondroitin compounds.
	2. 3 x 400 mg CS	randomized, placebo-controlled, double-blind 3 years	CS: 44 Plc: 48 after 3 yrs. CS: 34 Plc: 39	• X-ray DIP, PIP and MCP joints • 2 anatomical rating systems • VAS		

Study	Daily dose**	Study design	Pts. (n)	Parameters	Results	Authors' conclusion
TMJ osteoarthritis						
Shankland 1998[119]	2 x 1,200 mg CS-4 / CS-6, 2 x 1,600 mg GHCl 2 x 1,000 mg Ca-ascorbate (analgesics: IBU, ASS as needed)	open trial (pilot study)	50 pts. 4 M, 46 F	• TMJ noise • Pain • Swelling	• 80% (40 pts.) reported a reduction of the TMJ noise • Reduction of symptoms within the first 2 weeks • Also improvement in other joints (knee, hip, sacroiliac joints)	Interestingly there were clinical improvements regarding symptoms in the knee, hip and sacroiliac joints.
Meta-analyses (knee osteoarthritis)						
Leeb et al. 2000[71]	800-2,000 mg CS (+ concurrent NSAIDs)	double-blind 90-365 days	7 studies selected (out of 16) between 1992 and 1998: 372 pts.	• Lequesne index • Pain (VAS)	• **CS** was significantly superior to Plc with relation to Lequesne index and in pain score (VAS) • At least 50% improvement in study variables for the CS group vs Plc	CS has proven favorable for the dietary management of OA. But further studies including larger patient groups and with a longer study duration are necessary.
Richy et al. 2003[102]	1,500 mg GS 800-2,000 mg CS (+ concurrent NSAIDs)	randomized, placebo-controlled, double-blind GS: 4 wks to 3 yrs CS: 90-365 days	7 studies with GS 8 studies with CS between 1980 and 2002 1,775 pts.	• JSN • Lequesne index • WOMAC • Pain (VAS) • Mobility • Safety • Response rate	• **GS:** improvement in all variables, incl. JSN and WOMAC • **CS:** effective with relation to Lequesne index score, pain VAS score, mobility and response rate • **For both:** excellent safety	For **GS** there is evidence of structural efficacy, for **CS** evidence of symptomatic efficacy.

Abbreviations:

AFI	Lequesne algofunctional index
CS	chondroitin sulphate
So-CS	sodium chondroitin sulphate
CPS	chondroitin polysulphate
DIP	distal interphalangeal joints
F	females
GS	glucosamine sulphate
GHCl	glucosamine hydrochloride
HAQ	health-associated quality of life
IBU	ibuprofen
ISK	index of severity for osteoarthritis of the knee by Lequesne
ITT	intention-to-treat group
JS	joint space
JSW	joint space width
JSN	joint space narrowing
M	males
MCP	metacarpophalangeal joints
OA	osteoarthritis
PIP	proximal interphalangeal joints
Plc	Placebo
pts.	patients
TMJ	temporomandibular joint
VAS	visual analog scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Hyaluronic acid

Hyaluronic acid is a linear, long-chain polymer that is composed of the basic units D-glucuronic acid and N-acetyl-D-glucosamine (Fig. 9). These units may repeat themselves up to 50,000 times.[142]

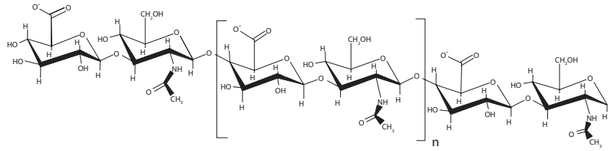


Fig. 9. Structure of hyaluronic acid = glucuronic acid β1,3-N-acetyl glucosamine (adapted from Wohlrab et al. 2004)[142]

The word hyaluronic acid is derived from the term glucuronic acid and the Greek word for "vitrous", i.e. hyaloid. The latter is related to the occurrence of hyaluronic acid in the vitrous body of the eye.

Hyaluronic acid is also an important component of various tissues, such as the:

- connective tissue
- synovial fluid (fluid from the cavities of synovial joints)
- fluid from the chamber of the eye
- skin
- hyaline cartilage
- umbilical cord

Hyaluronic acid determines the characteristics of the synovial fluid, the fluid of the chamber of the eye and the lymphatic fluid. The ability of hyaluronic acid to bind water lends it viscoelastic properties. This means that it is compressible and will return to its original shape as soon as the compression force is removed. These features enable hyaluronic acid to be used in numerous therapeutic fields. For example, it is used as an injectable solution in orthopedics for the treatment of osteoarthritis, and in cosmetic surgery it is suitable for facial injections as treatment for wrinkles, skin contours and lips. It is additionally available in the form of artificial tears and as a wetting agent for the eyes, and in cosmetic products, e.g. creams, as a moisturizing agent, and for promoting wound healing. Hyaluronic acid is also used as a filler material for breast or intervertebral implants.[142]

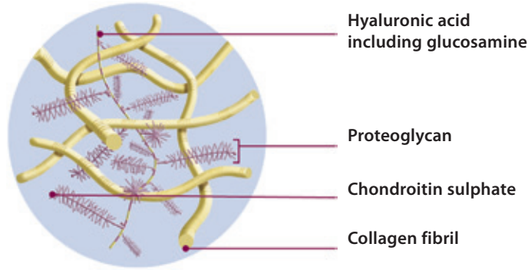


Fig. 10. Extracellular cartilage matrix

Function of hyaluronic acid in the cartilage tissue

The extracellular cartilage matrix is composed of collagen fibers and proteoglycans, in particular hyaluronic acid; these form the "backbone" of the cartilage tissue (Fig. 10).

Hyaluronic acid, along with chondroitin sulphate, is a member of the glycosaminoglycans substance group and is thus an amino sugar that is synthesized in cartilage cells, for example.

Hyaluronic acid is responsible for the viscoelastic quality of the synovial fluid. By storing and reversibly releasing water under load, hyaluronic acid promotes the elasticity of the joint cartilage.[37]

Degenerative and inflammatory processes induced by osteoarthritis may alter both the quantity and quality of hyaluronic acid in the synovial fluid and damage the joint cartilage.[37] The intra-articular injection of hyaluronic acid increases the level of hyaluronic acid in the synovial fluid, boosts the cartilage metabolism and reduces the production and activity of pro-inflammatory mediators as well as cartilage-degrading metalloproteases.[80] The efficacy and

tolerability of intra-articularly administered hyaluronic acid for the treatment of osteoarthritis pain has been proven in several clinical trials.[80]

Hyaluronic acid reaches joints when administered orally

Schauss et al. (1999) studied the absorption, distribution and elimination of radioactively labeled hyaluronic acid in dogs (beagles) and rats, and were able to show that hyaluronic acid is absorbed after a single oral dose and reaches the inner organs as well as the joints.[107]

Currently, no studies are available on the intake, distribution, metabolization and elimination of hyaluronic acid in humans. For such studies radioactively labeled agents are required, the use of which is prohibited in humans for ethical reasons. Consequently, kinetics in humans are essentially studied on the basis of conclusive animal models.

Efficacy of hyaluronic acid (oral administration)

In a clinical study by Bergin et al. (2006)[9] in horses (one-year-old thoroughbreds = yearlings) the efficacy, i.e. ability of oral hyaluronic acid treatment to reduce joint effusion was assessed. For this study, 48 yearlings with uni- or bilateral osteochondrosis dissecans (OCD)* of the tarsocrural joint (with a total of 57 affected joints) were selected that had only slight or absent joint effusions prior to the correcting arthroscopic surgery. After the surgery the animals were randomly subdivided into 2 groups of 24 each and treated with either 100 mg of oral hyaluronic acid per day or a placebo for the duration of 30 days.

30 days after the operation, an examiner scored the effusion of the tarsocrural joint using a scale of 0 to 5 (0 = no effusion, 1 = barely palpable effusion, 2 = palpable effusion, 3 = golf ball-sized effusion with plantar effusion, 4 = tennis ball-sized effusion with plantar effusion, 5 = > tennis ball-sized effusion with plantar effusion).

* OCD: disease of joint cartilage based on a disturbance of cartilage growth with formation of free bodies within the joint

Half grades were allowed, and OCD lesion sizes and locations were compared. With a total of 57 joints, the mean effusion score of the group that received treatment with hyaluronic acid for 30 days was 0.67 (vs. 2.05 in the placebo group; $p \leq 0.0001$).

Significant differences were also measured in the comparison of the OCD lesions of identical location and/or identical severity ≤ 1 cm or > 1 cm between yearlings treated with hyaluronic acid and those treated with a placebo (Fig. 11).

This study provides nutritional evidence of the efficacy of orally administered hyaluronic acid regarding the reduction of post-surgical joint effusions after arthroscopic removal of free bodies in the tarsocrural joint of horses with osteochondrosis dissecans.[9]

Oral administration of hyaluronic acid reduces post-operative effusion in the equine tarsocrural jointe

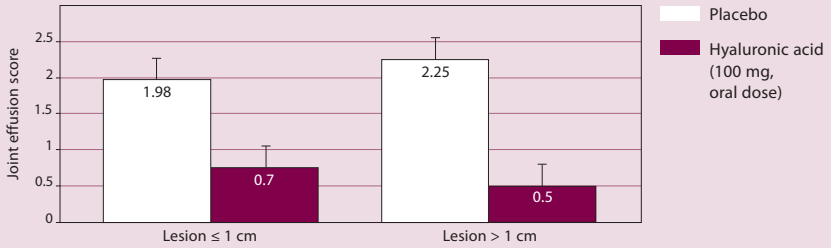


Fig. 11. Mean score of joint effusions in the HA group and placebo group for the joints including lesion sizes of ≤ 1 cm or > 1 cm ($p < 0.0001$ or $p < 0.0032$) respectively; adapted from Bergin BJ, et al. 2006[9]

Collagen hydrolysate

Basic facts. The cartilage tissue is subject to continuous remodeling, with alternating anabolic and catabolic processes (Fig. 14). Matrix components, such as collagen and proteoglycans, and polypeptide mediators (IGF, TGF and others) are important for the anabolic part of the system as they act as growth factors. Cartilage degradation is promoted by metalloproteinases and other substances that stimulate the catabolism (TNF-α, free radicals, etc.).

The supply of the components proline and glycine is particularly important for the formation of collagen in the cartilage matrix. They are 'semi-essential' amino acids which must be sourced externally under certain circumstances, e.g. when the joints are under severe strain, and are indispensable for functional, healthy joint cartilage.

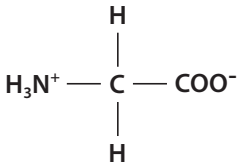


Fig. 12. Glycine

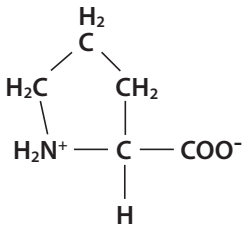
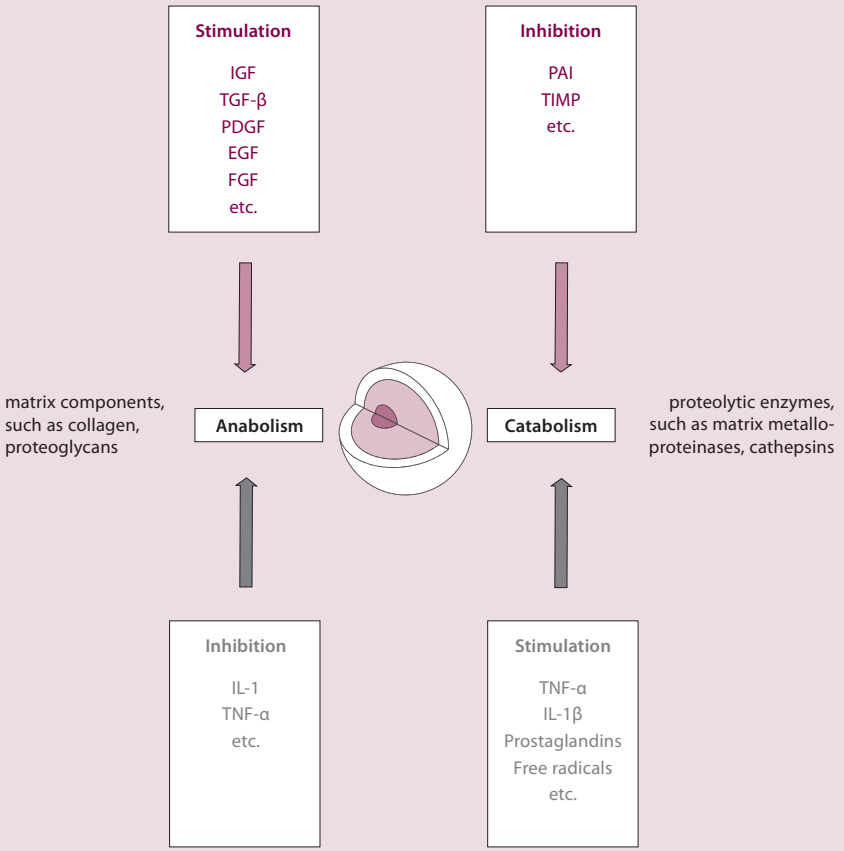


Fig. 13. Proline

Collagen hydrolysate is made enzymatically from natural collagen.
It contains the conditionally essential amino acids proline and glycine in a concentration three times as high as the concentration of other proteins. The mean molecular weight of the existing peptides amounts to 3 kDa on average, a condition that supports the intestinal absorption. Hydrolysate has good bioavailability.



Abbreviations:
IGF: insulin growth factor
PAI: plasminogen activator inhibitor
TGF β: transforming growth factor β
TNF α: tumor necrose factor α
EGF: epidermal growth factor
PDGF: platelet-derived growth factor
TIMP: tissue inhibitor of metalloproteinases

Fig. 14. Schematic image of cartilage metabolism[44]

We know from basic studies that, after absorption, collagen hydrolysate is taken from the blood circulation system and accumulated primarily in the cartilage where it stimulates the formation of new collagen in the chondrocytes.

Important in-vitro and in-vivo results. Collagen hydrolysate is not resistant to proteolytic enzymes, and (as with collagen) a large percentage (85-95%) is digested. This ensures that the components can be well absorbed.

In an animal experiment it was shown that after intragastric administration of radioactively labeled collagen hydrolysate, a larger amount of peptides thus labeled can be detected in the cartilage tissue.[89] In that study, mice were given radioactively labeled collagen hydrolysate (or labeled proline as a control) with a dose of 10 mg per gram of body weight. After 3 to 96 hours the radioactivity was measured in various tissues. Whereas in the plasma the radioactivity had degraded after 96 hours, it had accumulated significantly in the joint cartilage.

Recent studies show that after the enrichment of a bovine cartilage cell culture with collagen hydrolysate, the biosynthesis of type-II collagen in the chondrocytes was markedly increased. In the same way, a significant increase in aggrecan, a proteoglycan, can be observed.[90]

Clinical studies. Besides the good experiences gained in medical practice, there are also a number of clinical studies on collagen hydrolysate available which deal with demonstrable dietary effects of collagen hydrolysate on pain intensity, consumption of analgesics, mobility and physiological function. All studies show a trend towards favorable effects of collagen hydrolysate in patients with osteoarthritic joint alterations.

The two most important studies published so far have produced the following results:

– Adam[1] published a randomized, double-blind study including 81 patients. Four different forms of dietary therapy with collagen hydrolysate vs a placebo were studied, with a two-month wash-out phase before each two-month therapy phase with collagen hydrolysate or chicken protein as a placebo (total duration 16 months). A total of 52 patients were given all 4 forms of treatment in different sequences. The evaluation showed that the dietary treatment with collagen hydrolysate compared to the control group led to a markedly more effective pain reduction. Thus, in 48.1% of the patients the pain score with collagen hydrolysate intake dropped significantly by ≥50%. Moreover, 69.8% of the patients were able to lower their consumption of analgesics by 50% (Fig. 15).

Collagen hydrolysate nutritionally reduces pain and consumption of analgesics

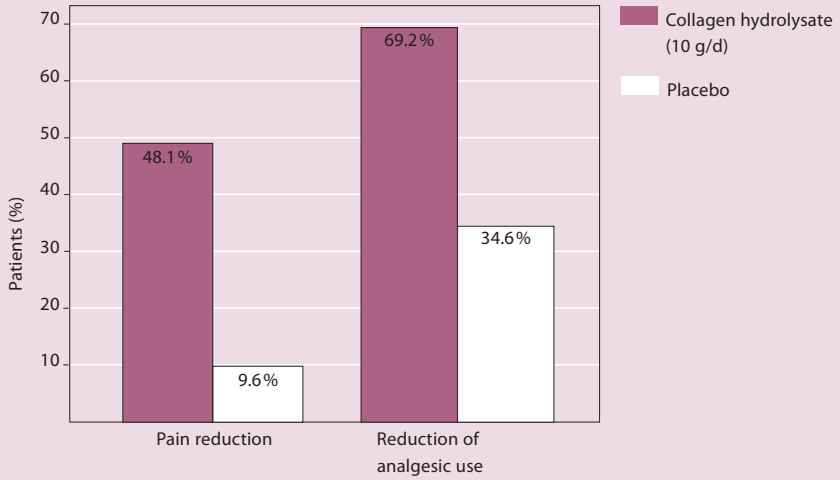


Fig. 15. Relief and reduction of analgesic use by ≥50% each[1]

- Probably the most comprehensive trial was made by Roland W. Moskowitz, a rheumatologist.[82] This multi-center, randomized trial was held in 1996-98 over a treatment period of 24 weeks at 19 centers in the USA, the U.K., and Germany. The comparison included a total of 389 patients with manifest knee-joint osteoarthritis. Based on the pain score, the joint function improvement and the patients' overall response to the therapy, the positive efficacy of collagen hydrolysate could be confirmed, although there were big differences in the three countries that participated in the trial. In the German patient group the favorable results were particularly impressive: the patients reported both reduced pain in the osteoarthritic knee joint and an improvement in the joint function. The difference in the results of the three countries was to be explained by the difference in the concomitant medication (especially analgesics) and higher drop-out rates.

Prospects. In a new study submitted for publication[144] 190 patients with mild osteoarthritic symptoms of the knee joint were treated for 14 weeks with either a combination of 10 g of collagen hydrolysate, 300 mg of calcium and 60 mg of vitamin C, or with a placebo. After that period the patients in the collagen hydrolysate group demonstrated an improvement in the isometric and isokinetic strength of the knee joint and the total work performance in comparison to the placebo group.

Other studies, some of them not randomized, and empirical reports[66] indicate the efficacy and safety of collagen hydrolysate as a supplement with a preventive effect and as a dietary therapeutic adjunct for patients with osteoarthritis.

Tolerability of collagen hydrolysate. The US Food and Drug Administration (FDA) has recognized collagen and hydrolyzed collagen products as safe for human health and granted them the GRAS status ("generally recognized as safe").

In the Moskowitz study quoted above, none of the subjects showed any side effects that could be attributed to the increased consumption of collagen hydrolysate.

- Collagen hydrolysate is neither mutagenic nor teratogenic.
- Collagen hydrolysate is hypoallergic and can therefore even be used as a plasma expander. No other findings for oral administration have become known in Europe and North America. The risk is therefore negligible.
- Interactions with other foods or drugs are not known.
- When collagen hydrolysate is produced from bovine bone and the middle layer of bovine skin, both hydrochloric acid and sodium hydroxide are used (over several weeks) and, in addition, the filtered extract is sterilized at more than 140 °C. Any BSE pathogens that might be present are destroyed in the process.

N-acetylcysteine

In cysteine metabolism, sulphate is formed that serves the connective and supporting tissues for the biosynthesis of sulphated mucopolysaccharides and is important for the treatment of osteoarthritis. The fact that the cartilage-regenerating proteoglycan synthesis is enhanced by methionine, glucosamine and chondroitin sulphate supplements has been confirmed in humans.[23] There are indications in human studies which show that sulphate is indispensable for the physiological effect of glucosamine.[58]

Table 6. Nutritional features and characteristics of collagen hydrolysate and N-acetylcysteine

Collagen hydrolysate
Support of cartilage metabolism
Proline and glycine are important structural components for collagen formation in the cartilage matrix → in chondrocytes, in particular the formation of type II collagen and of the aggrecan proteoglycan is promoted
Positive effects on symptoms
relieves joint pain in osteoarthritic patients[1]
under collagen hydrolysate treatment simultaneously less need for NSAIDs[1]
N-acetylcysteine
Support of cartilage metabolism
involved in the formation of sulphate groups[23] → formation of sulphated mucopolysaccharides

Micronutrients and their nutritional influence on joint processes

Besides chondroprotective substances, other micronutrients, such as vitamins, minerals and trace elements, as well as essential fatty acids, also play a crucial role in the osteoarthritic process. The following chapters offer an overview of the features and special characteristics of omega-3 fatty acids and micronutrients. This information serves to underline the importance of such substances for the joint metabolism from a nutritional point of view.

Omega-3 fatty acids

The inflammatory mediators in both activated osteoarthritis and rheumatoid arthritis are products of the same metabolic pathways. Thus, similar points of attack for omega-3 fatty acids are present in the inflammatory episodes of activated osteoarthritis. A number of studies have documented the favorable effect of omega-3 fatty acids on inflammatory processes that play a role in the development of osteoarthritis.[26-28]
The biochemical approach here is the arachidonic acid cascade and the antipole formation with omega-3 fatty acids, especially eicosapentaenoic acid.[79] The essential inflammatory mediators – the eicosanoids thromboxan A_2, prostaglandin E_2 and leukotriene B_4 – can be detected in acutely inflamed joints. They are formed from arachidonic acid with the help of the enzymes lipoxygenase and cyclooxygenase. Eicosapentaenoic acid (EPA) inhibits the transformation of arachidonic acid to the proinflammatory eicosanoids mentioned once it has been incorporated in the phospholipids of the cell membrane[126] (see also Fig. 17). EPA reduces the activity of the phospholipase A_2,[30] which splits diacylglyceride and thus releases arachidonic acid from the cell membrane. The body's own synthesis of arachidonic acid from linoleic acid is also markedly reduced by EPA.[59]
This effect can be observed after intake of NSAIDs as well. Inflammation-inhibiting eicosanoids are formed from EPA. In addition, EPA reduces the

production of the tumor necrosis factor α and interleukin-1α and -1β, which in their turn stimulate collagen degradation via metalloproteinases.[26,79] Unlike omega-6 fatty acids, the addition of omega-3 fatty acids to the cell culture led to a **reduction in endogenous aggrecanases and collagenases**.[28] The concentration of these cartilage-degrading enzymes in the blood and in the synovial fluid is increased in inflamed joints.[79] Also the cartilage-degrading metalloproteinases were lowered in vitro by omega-3 fatty acids. [27,28] Therefore, omega-3 fatty acids may have both a symptom-modifying and a structure-modifying chondroprotective effect.

Table 7. Nutritional features and characteristics of omega-3 fatty acids

Omega-3 fatty acids
Inhibition of degradation processes in the cartilage
EPA inhibits the formation of the tumor necrosis factor α and of interleukin-1α and -1β → reduce collagen degradation[28]
Anti-inflammatory
decelerate and reduce inflammatory processes[26-28]

Antioxidants

Diseases of the joint, such as osteoarthritis and rheumatoid arthritis, are characterized by the increased formation of free radicals.[55] A high nitrite/nitrate concentration was detected in the synovial fluid of osteoarthritic patients. Therefore, the influence of free radicals on the pathogenesis of osteoarthritis has been studied by several authors.

It was found that free radicals have a detrimental effect on the cartilage metabolism and thus influence basic processes, such as cell activation and proliferation. In this way they cause structural and functional damage to the cartilage. Free radicals are also responsible for the increased expression of metalloproteinases, collagenases and gelatinases which contribute to matrix degeneration.[56] Moreover, they inhibit the proteoglycan synthesis, and the chondrocytes lose their ability to respond to growth factors.[55]

In order to avert the toxic impact of the free radicals, the cartilage cells have a well-organized oxidative system including superoxide dismutase, catalases and glutathione peroxidase.[56] In-vitro and in-vivo studies have shown that elevated oxidative stress caused by osteoarthritis can reduce the antioxidant capacity of the joint cartilage with resulting damage to the chromosome ends ('telomeres'), functional disturbances and aging of the cartilage cells, and catabolic changes in the cartilage matrix.
In contrast, the treatment of cartilage explants with antioxidants has led to lengthening of the telomeres and the replication cycle of cultivated cartilage cells.[143]

The antioxidant vitamins C, E, A, mixed carotenoids and citrus bioflavonoids, protect the cells against the harmful effects of prooxidants.[45]

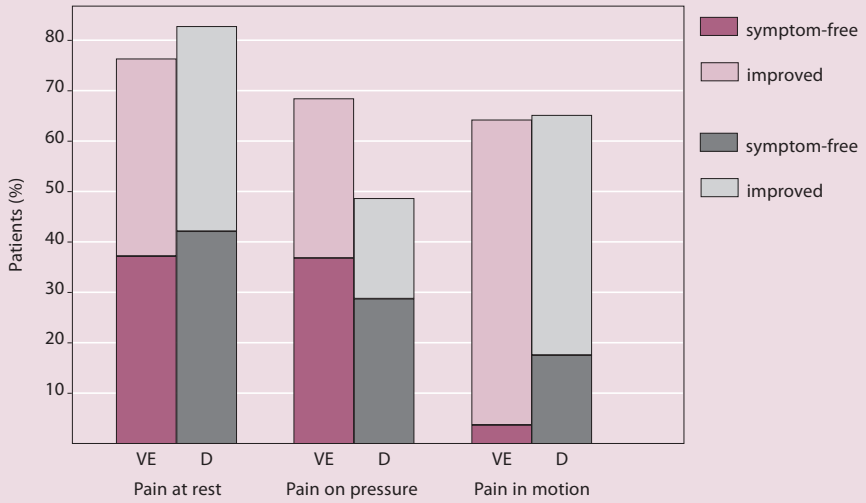
Vitamin A. Besides having an antioxidant effect, retinol can evidently inhibit cartilage and collagen degradation, bone resorption and the acute inflammatory process. Thus, several studies with patients suffering from acute rheumatoid arthritis[102,121,122] or osteoarthritis[57] were able to show that vitamin A and all-trans retinol acid[57] suppressed the expression and activity of certain matrix metalloproteinases. The vitamin also reduced the formation of interleukin-1 und TNF-α in the chondrocytes.[57]

Vitamin E. Vitamin E is a lipophilic oxygen radical scavenger. In-vitro studies and animal models have shown that vitamin E promotes the growth of chondrocytes, protects against free radicals and thus counteracts the development of osteoarthritis.[63,127] In another study, administration of vitamin E inhibited the increase in free radicals associated with arthritis. Moreover, the vitamin has an anti-inflammatory effect because it can reduce the release of arachidonic acid and the activity of lipoxygenase and cyclooxygenase.[10,108] (see also Fig. 17).

A number of short-term studies with humans demonstrate the structural effect of vitamin E on osteoarthritis and rheumatoid arthritis. Thus, a vitamin E supplement improved parameters such as pain caused by pressure,[11] morning stiffness[54] and pain when in motion.[5]

In a randomized, single-blinded study, 29 osteoarthritis patients took either 600 mg of vitamin E or a placebo every day for 10 days. Fifty-two percent of the patients who had taken vitamin E and only 4% of the patients in the placebo group reported a pain reduction ($p<0.01$).[74] In another study, 53 patients with knee or hip joint osteoarthritis took 400 mg of vitamin E or 150 mg of diclofenac 3 times per day for 3 weeks. The intake of vitamin E led to a reduction in the pain when resting, upon pressure or in motion by 77%, 67% and 62%, respectively, and was comparable to the analgesic effect of diclofenac (Fig. 16). In both groups, a significant decrease in the knee joint circumference ($p = 0.001$), an improvement in knee and

Pain relief with vitamin E compared to diclofenac



VE = vitamin E (400 mg t.i.d.) D = diclofenac sodium (50 mg t.i.d.)

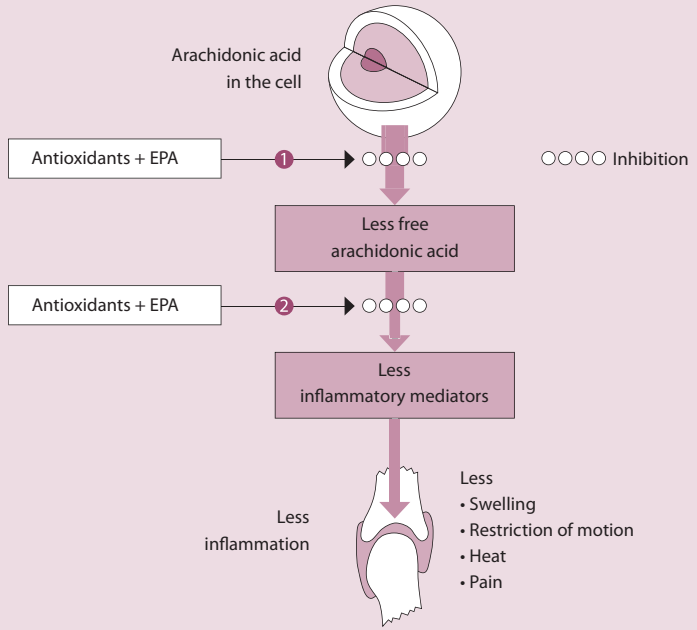
Fig. 16. Changes of pain at rest, upon pressure and in motion with vitamin E vs. diclofenac; modified after Scherak et al.[109]

hip joint mobility ($p = 0.002$) and a lengthening of the gait distance was observed[109] ($p < 0.001$). Wittenborg et al.[141] could not show any significant difference between vitamin E and NSAID intake either (measuring parameters: morning stiffness, strength of grip, pain intensity). Other studies indicate that with vitamin E supplementation the intake of NSAIDs can be lowered.[2,3,12]

Vitamin C. Vitamin C promotes the regeneration of the vitamin E that was itself oxidized by the inactivation of oxygen radicals.[30,43]
Vitamin C is also involved in the synthesis of the collagenous connective tissue and is therefore indispensable for the regeneration of cartilage and bone.[48] Under the influence of vitamin C chondroitin sulphate controls the production and stabilization of collagen.[110] In an experiment with guinea pigs, vitamin C protected against experimentally induced cartilage degradation[78] (quoted in Gaby[45]). In other animal studies, an elevated concentration of the vitamin was measured in the cartilage and synovial fluid after administration of vitamin C.[123] McNulty et al.[77] showed the proactive transport of vitamin C to the cartilage.

Studies with humans have also shown that vitamin C counteracts the development of osteoarthritis. In the 'osteoarthritis' cohort of the Framingham Study in which 640 subjects were followed up over a period of 9 years, the moderate intake of 120-200 mg of vitamin C per day led to a significantly, i.e. 3 times, lower risk of osteoarthritis progression. Cartilage degradation was also reduced. Moreover, high vitamin C intake lowered the probability of developing pain in the knees.[76] The study by Pattison et al.[92] including a total of 25,663 subjects from 1993 until 1997 also demonstrated an elevated risk of inflammatory joint diseases in subjects with a lower consumption of fruit and/or fruit + vegetables.

An inverse relationship was found to exist for vitamin C between intake and arthritis risk. Thus, subjects in the lowest tercile of daily intake had a risk that was over 3 times higher of developing an inflammatory joint disease (1st tercile: < 55.7 mg OR_{korr} 3.3; 2nd tercile: 55.7-94.9 mg OR_{korr} 0.8; 3rd tercile: > 94.9 mg OR_{korr} 1.0; $p = 0.01$).



Antioxidants can affect the inflammatory response at two sites:
1 via enzymatic activity of phospholipase A, and
2 via transformation of ARA to inflammatory mediators.

Fig. 17 Antiinflammatory effects of antioxidants and eicosapentaenoic acid (EPA)

In a randomized, placebo-controlled, multi-center, cross-over trial[60] the pain-reducing effect of vitamin C could also be demonstrated. This trial included 133 osteoarthritis patients. The 14-day consumption of 1 g of calcium ascorbate per day, which included 898 mg of vitamin C, reduced the pain significantly in comparison with the placebo ($p = 0.0078$). The Lequesne score also improved after calcium ascorbate intake ($p = 0.036$; difference: 0.56).

In summary, the antioxidant vitamins E and C, as well as carotenoids such as beta-carotene and lutein, have a high antioxidant potential based on their synergistic effect.[30] Antioxidants can therefore reduce oxidative stress and exert a positive influence on the inflammatory reactions in osteoarthritis. In studies on rheumatoid arthritis in which a combination of fish oil and antioxidants (vitamins E, A, C, selenium) was given, a favorable effect on the inflammatory process and a resulting influence on the symptoms could be documented.[51,134]

Table 8. Nutritional features and characteristics of antioxidants (vitamins A, E, C, carotenoids, citrus bioflavonoids)

Antioxidants
antioxidant, strong radical scavengers → protection of joints against oxidative stress involved in collagen metabolism (vitamin C) positive influence on symptoms[60,108]

Minerals and trace elements

Calcium. The most important element in the bone metabolism is calcium. Calcium makes the bones firm. Adults have a total of 1.0-1.5 kg of calcium, 99% of which is contained in the bones and teeth. Only 1% of the calcium is needed for active metabolism. Every day between 250 mg and 500 mg of calcium are released from and taken up again by the bone as a result of remodeling processes.

Besides cartilage and ligaments, the bony components make up most of the joints. In osteoarthritis patients the bone tissue underneath the compromised joint cartilage layer is also affected.

In the development of osteoarthritis, calcium is bound to the sulphate groups of chondroitin sulphate. The degradation of chondroitin sulphate in osteoarthritis thus has a negative effect on calcium absorption and calcium binding and thus prevents the stabilizing effect of calcium. The intake of vitamin D and calcium with the diet can counteract this negative effect.

In studies, the osteoarthritis symptoms could be reduced by giving the patients a combination of calcium and vitamin C.[119]

Manganese. Manganese is a component of enzymes (glycosyl- and xylosyltransferases) which are responsible for the glycosidic binding, and thus synthesis, of glycosaminoglycans. Moreover, manganese is involved in the cross-linkage of collagen fibers and inhibits elastases which degrade collagen and elastin.[85] In animal studies it was shown that manganese also plays a role in the synthesis of chondroitin sulphate.[45]

As a cofactor of superoxide dismutase, manganese also prevents oxidative joint damage and thus counteracts the osteoarthritis-related degradation of the cartilage matrix. The combination of glucosamine sulphate, chondroitin sulphate and manganese ascorbate[8,31] has proved to be particularly effective in osteoarthritis management. In a study with rabbits the combination of glucosamine, chondroitin sulphate and manganese ascorbate counteracted cartilage degeneration more effectively than the administration of each individual substance alone.[73] In a trial by Leffler et al. a dose of 1.5 g of glucosamine sulphate, 1.2 g of chondroitin sulphate and 228 mg of manganese ascorbate was very well tolerated by all subjects over a period of 8 weeks.[72]

Selenium. Selenium is a component of glutathione peroxidase which is part of the endogenous antioxidant protection system and protects macromolecules against oxidative stress. Sodium selenate inhibits lipid peroxidation in the presence of an elevated glutathione peroxidase activity and in this way reduces the formation of pro-inflammatory eicosanoids.[53]

Zinc. As a result of its antioxidant and anti-inflammatory effect, zinc has a protective role in the development of osteoarthritis. In the case of a selenium, calcium and zinc deficiency Kashin-Beck disease will develop, which is a form of arthritis with skeleton deformations that occurs in humans and animals.[140]

Moreover, low zinc concentrations have often been found in patients with osteoarthritis. Zinc deficiency causes a retardation of the skeleton growth and also is a risk factor for osteoporosis.[46]

Copper. Copper is an essential component of lysyl oxidase which is involved in the cross-linkage of collagen and elastin in cartilage and bone. Copper, as a component of aminoxidase, also plays a role in the biosynthesis of glucosamine. As a component of Zn-Cu superoxide dismutase, copper helps eliminate peroxide radicals.

Molybdenum. Molybdenum is a cofactor of sulphite oxidase which produces sulphates that are important for proteoglycan synthesis. In the case of a molybdenum deficiency, less sulphate is obtained from the sulfhydryl groups of the sulphurous amino acids, causing the impairment of proteoglycan synthesis.

Table 9. Nutritional features and characteristics of minerals and trace elements

Calcium
central element in bone metabolism, key mineral in bones and teeth

Manganese
component of enzymes which are responsible for the formation of cartilage components
contributes to the cross-linking of collagen fibrils

Selenium
component of antioxidant enzymes

Zinc
component of numerous enzymes
part of the endogenous antioxidant protection system, protection against radicals
anti-inflammatory

Copper
component of antioxidant enzymes
component of enzymes which are responsible for the formation of cartilage components

Molybdenum
component of enzymes which are responsible for the formation of cartilage components

Other micronutrients

The vitamins described here are not only important for the cartilage metabolism and thus the treatment of osteoarthritis, but also for the joint in general. In particular, vitamins K_1, D and B_6 with their nutritional features and characteristics play an important role in osteogenesis.

Vitamin D. Vitamin D is used as a result of its positive effect on bone metabolism. It not only has a favorable influence on the calcium metabolism, but also plays a crucial role in the cartilage metabolism. Fairney et al.[38] were able to show that the synovial fluid contains significant quantities of 25-OHD, 24,25$(OH)_2D_3$ and the vitamin D binding protein. A less than optimal supply of vitamin D has a negative effect on the calcium metabolism, osteoblast activity, bone matrix mineralization (ossification), bone density, and cartilage metabolism.[111] (Corvol et al.[24], Dean et al.[32], Parfitt et al.[91] quoted in Wang et al.[139]). In chondrocyte cultures vitamin D stimulates the proteoglycan synthesis and thus has a direct influence on the formation of joint cartilage (Gerstenfeld et al.[47] quoted in Wang et al.[139]). Furthermore, Schwartz et al.[112] documented that vitamin D_3 metabolites have an influence on the proliferation and differentiation of cartilage cells.

A prospective trial with 237 subjects extending over more than 8 years showed that low 25-hydroxy vitamin D concentrations were associated with a 3-fold higher hip joint osteoarthritis risk.[69] A part of the Framingham Study including 556 osteoarthritis patients and subjects with healthy joints demonstrated a 3-fold higher progression risk in those subjects who only took low to medium quantities of vitamin D. A low vitamin D level in the blood was associated with a narrowing of the joint cavity that occurred 2.3 times more often and a 3.1 times greater osteophyte growth.

These studies prove that an adequate intake of vitamin D will slow down the progression of osteoarthritis and can protect against the development of the disease.[45] In addition, active vitamin D metabolites perform important immunomodulatory functions, and in inflammatory processes these are also anti-inflammatory.[52]

Vitamin B complex. As cofactors of many enzymes, the B vitamins are essential to the metabolism, including that of the bone. Thus, Carmel et al.[18] documented that the osteoblast activity depends on **vitamin B_{12}** (cobalamin) and that bone metabolism will be adversely affected by a vitamin B_{12} deficiency. Necessary supplementation was given to subjects who were deficient in vitamin B_{12}. As a result, the osteocalcine concentration in the blood increased. This protein, which depends on vitamin K synthesis, is only synthesized by osteoblasts and serves as a marker of an increased osteoblast activity. Moreover, the level of the bone-specific alkaline phosphatase that is typical of osteoblasts rose. A basic supply of B vitamins should therefore be provided to ensure osteoblast function.

A number of studies show that nicotinamide, folic acid and vitamin B_{12} have a favorable effect on osteoarthritis symptoms.[139] Some authors could prove, for instance, that the intake of nicotinamide (from 900 mg to 4 g per day) improved joint mobility and reduced joint inflammation and pain after only 3 to 4 weeks.

In a placebo-controlled, double-blind trial with 72 patients taking 3 g of **nicotinamide** or a placebo every day for a period of 12 weeks, the osteoarthritis symptoms improved (AIMS, Fig. 18) by 29%.[62] In the placebo group, however, the symptoms were aggravated by 10%. Although the pain remained the same, the consumption of anti-inflammatory drugs in the nicotinamide group could be lowered by 13% ($p = 0.01$). Nicotinamide also decreased the blood sedimentation rate by 22% ($p < 0.005$). Joint mobility improved after administration of nicotinamide (by 4.5°) compared to the control group (8° vs 3.5°; $p = 0.04$).[62]

Most important results in selected osteoarthritis parameters

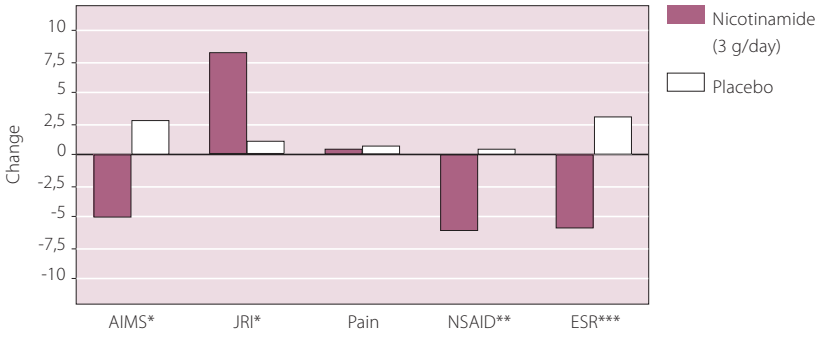


Fig. 18. Absolute changes vs. baseline after 12-week nicotinamide treatment; modified after Jonas et al.[62]

AIMS = Arthritis Impact Measurement Scales (score); **JRI** = Joint Range Index (degree); Pain (AIMS subscale, score); **NSAID** (pill-equivalents per month); **ESR** = erythrocyte sedimentation rate (mm/h). * $p<0.04$; ** $p<0.01$; *** $p<0.004$ modified after Jonas et al.[62]

A controlled, double-blind, cross-over study dealt with the effect of **folic acid and vitamin B_{12}** supplementation in 26 subjects who had already suffered from osteoarthritis of the hand and finger joints for 5.7 years. They were given either 6.4 mg of folic acid plus 20 µg of vitamin B_{12} or a placebo daily for 2 months. After taking the B vitamin the strength of grip of the hands increased. Besides, the effects of the folic acid and vitamin B_{12} supplementation were comparable with those of NSAID therapy. With NSAIDs the number of hand and finger joints that were tender on pressure was greater than with the folic acid + vitamin B_{12} combination.[41]

Other studies prove that the additional intake of large amounts of **vitamin B (B_1, B_6 und B_{12})** will enhance the effect of NSAID therapy by dietary managment.[15,67,68]

Vitamin B_6 – just as vitamin C – also plays a role in the connective tissue metabolism, especially in collagen synthesis. As cofactor of lysyl oxidase it contributes to the cross-linkage of collagen und elastin.

Vitamin K. In addition to blood coagulation, vitamin K is very important for the bone metabolism because, as a cofactor, it is involved in the gamma-carboxylation of glutamine residues. These carboxylated compounds are used in the synthesis of osteocalcine – which, after collagen, is the most important bone protein – in the osteoblasts. In two studies a connection was found to exist between a low vitamin K intake and a significantly lower bone mineral density (BMD).[13,64]

Table 10. Nutritional features and characteristics of vitamin D, B vitamins and vitamin K

Vitamin D
has an essential effect on calcium metabolism
contributes to cartilage metabolism

Vitamins of the B complex
contribute to connective-tissue metabolism (vitamin B_6)
relief of osteoarthritic symptoms (vitamin B_{12}, folic acid, nicotinamide)

Vitamin K
involved in bone metabolism

Pharmaceuticals and micronutrients

When a patient is treated with NSAIDs or corticoids over a longer period, the impact on their micronutrient supply must be considered.

It is possible

- **with NSAID therapy**[49,50,95]
  that a deficiency in vitamins K, C, B_1, B_6, of nicotinamide, folic acid, trace elements in general and iron, zinc and copper in particular, and
- **with corticoid therapy**[49,50,95]
  that a deficiency in vitamins D_3, C, B_6 and folic acid, calcium, manganese and the trace elements zinc and selenium will develop.

The administration of important micronutrients can therefore counteract such deficiencies by dietary management.

Summary

Osteoarthritis is a **multi-factorial disease** which ultimately leads to the **destruction of the cartilage tissue and to reactive bone tissue hypertrophy** in the affected joints. In the course of the disease the joint cavity will narrow until in the final stage the joint cartilage layer has completely disappeared. In the process the cross-linkages of the cartilage-forming biopolymers will disappear, which impairs the capability of the cartilage to bind water and act as a 'shock absorber'.

When supplying patients with important components of the proteoglycan and collagen synthesis, the principal aim is to **support the body's own repair processes** that are to stabilize the joint and improve the symptoms by remodeling the joint structures. In today's medical practice the greatest need is to reduce osteoarthritis symptoms, such as pain and restricted function. For this purpose, analgesics, non-steriodal anti-inflammatory drugs, muscle relaxants, joint injections with steroids and local anesthesia are used. Other therapeutic approaches include physiotherapy and ergotherapy, orthotic devices and patient education.

A **curative treatment** of osteoarthritis is still not possible. But in all stages of the disease and for all age groups dietary management consisting of a well-balanced combination of cartilage-protecting substances (SADOA) and micronutrients is available to support primary osteoarthritis therapy. In addition, these substances have synergistic properties with regard to their structure and symptom-modifying effects.

Osteoarthritis has multiple causes and takes many different courses, and the favorable nutritional characteristics of various micronutrients and cartilage components used in its treatment are just as varied:

- Support of the cartilage and bone metabolism
- Antioxidant effects
- Anti-inflammatory effects

As a result of these characteristics, they contribute to mitigating the symptoms and also to reducing the intake of NSAIDs.

Current studies already show that the research of anti-osteoarthritic drugs will be intensified in the future because they offer a useful addition to conventional osteoarthritis therapy.

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