Clinical Effects of the Dietary Management of Osteoarthritis Symptoms

Clinical Effects of the Dietary Management of Osteoarthritis Symptoms – Results of a Multicentered Observational Study

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Introduction

In Germany there are some 35 million people with radiologically confirmed osteoarthritis, 5 to 15 million of them suffer from osteoarthritis-mediated symptoms (1).

Etiopathogenetically, osteoarthritis is a multifactorial disease that develops as a result of congenital malpositions, uneven wear, or injuries. A progressing osteoarthritic process will lead to the increasing destruction of cartilage tissue. The associated pain and restriction of movement often cause the patient's immobilization, which will itself result in progressing symptoms in the sense of a vicious circle. The primary objective of any osteoarthritis therapy must therefore be to alleviate pain and keep the joints functional and mobile. In addition to weight reduction, physiotherapeutic measures and supportive drug therapy, there are a number of chondroprotective cartilage nutrients that can beneficially influence the disease process on the basis of nutritional medicine (2, 3). Glucosamine and chondroitin sulphate are the chondroprotective substances of principal interest.

Summary

Objective: Biochemical and clinical studies show that chondroprotective cartilage nutrients (glucosamine sulphate, chondroitin sulphate, collagen hydrolysate and hyaluronic acid) and specific micronutrients (omega-3 fatty acids, vitamins D, E, C, etc.) beneficially influence the osteoarthritic process. A multicentered observational study was to determine whether the controlled administration of a targeted combination of these compounds is associated with a clinical benefit for patients with knee osteoarthritis.

Materials and methods: A total of 450 patients, average age 58.7 ± 13.7 years, suffering from knee osteoarthritis stages I to IV according to Kellgren & Lawrence, received a dietary food for special medical purposes (Orthomol® Arthro plus) for a period of four months. Pain intensity and stiffness of the joint were assessed using the validated WOMAC Index. The quality of life, the frequency of analgesic intake and the use of concurrent treatments were recorded in a questionnaire.

Results and evaluation: In the course of the observational period during administration of the study product, a continuous and significant reduction in the WOMAC global score by 52.9 % (median t0 vs t4) or 40.5 % (mean value t0 vs t4; $p < 0.0001$) was observed, and patients with all stages of osteoarthritis benefited from the dietary management. During the controlled intake of the dietary food for special medical purposes the mean joint stiffness was significantly reduced by as much as 37.5 % (t0 vs t4; $p < 0.0001$).

While at the start of the study 44.9 % of patients required analgesics, their proportion dropped significantly in the following four months to 27.3 % ($p < 0.0001$). Moreover, an analysis of the group of patients who provided details on analgesic use showed that 44.3 % of these patients could reduce the analgesic dose. Concurrent treatments, such as physiotherapeutic therapies (t0: 39.3 % of patients; t4: 17.1 % of patients), were also administered to a lesser extent. In addition, the reduction in symptoms and intake of analgesics had an effect on the quality of life. 72 % of patients who reported an impaired quality of life at the start of the trial experienced an improvement in their quality of life four months later, at the end of the trial.

Key words: chondroitin sulphate, glucosamine sulphate, hyaluronic acid, collagen hydrolysate, osteoarthritis, dietary management

Glucosamine sulphate is an amino monosaccharide and as such a component of the glucosaminoglycans in the cartilage matrix. Besides the inhibiting effects on various matrix metalloproteases, glucosamine has anti-inflammatory properties that counteract the destruction of the cartilage matrix (2). A large number of clinical studies have now been completed that prove the benefit of an adjuvant dietary therapy including glucosamine sulphate preparations. The positive effects demonstrated include not only significant pain alleviation but also an improvement in joint mobility, a reduction in pressure sensitivity and a decrease in joint swelling (4, 5). Compared with non-steroidal anti-inflammatory drugs (NSAIDs), glucosamine sulphate showed a similar pain-alleviating effect and better tolerability (6, 7).

Besides glucosamine sulphate, chondroitin sulphate also is a component of the cartilage matrix that essentially contributes to the tensile strength of the cartilage tissue. The clinical benefit of the oral intake of chondroitin sulphate by osteoarthritis patients has been documented in a dozen clinical trials that were also evaluated by meta-analysis (8, 9). Patients with knee osteoarthritis who took oral chondroitin sulphate experienced a significant alleviation of pain (10) and a reduced need for NSAIDs (11). Better joint mobility and less joint swelling could also be demonstrated. In addition, chondroitin sulphate has a beneficial influence on the progression of knee osteoarthritis, as a trial including 46 patients was able to show. Whereas the medial joint space narrowed significantly within one year during administration of a placebo, it remained unchanged in patients who had taken 800 mg of chondroitin sulphate daily (12).

According to the results of a subgroup analysis of the GAIT study, the two chondroprotective substances obviously have a synergistic effect, which is another important finding. In that study, the combined administration of glucosamine and chondroitin led to a significant improvement in the joint function of the patient group with medium to severe pain (13).

Other nutrients can influence the course of the disease in a beneficial way as a result of their chondroprotective, antioxidant and anti-inflammatory effects. They include (2, 3):

- Collagen hydrolysate which stimulates the formation of cartilage matrix proteins, such as type-II collagen and aggrecan;
- Omega-3 fatty acids which inhibit the arachidonic acid cascade at several sites and thus suppress the formation of proinflammatory eicosanoids, such as thromboxane A_2, prostaglandin E_2 and leukotrien B_4;
- Vitamins E and C which, due to their antioxidant potential, can counteract the increased formation of free radicals observed in osteoarthritic patients.

In addition, calcium, vitamins K_1 and D_3 together with the trace elements manganese, molybdenum, copper, zinc and selenium, are also closely connected with the bone metabolism of the cartilage and joint.

Table 1: Composition of study product Orthomol® Arthro plus

Nutrients	per daily serving	per 100 g
Amino Sugars		
Glucosamine sulphate	1,100 mg	6.7 g
Chondroitin sulphate	400 mg	2.4 g
Hyaluronic Acid	50 mg	303 mg
Amino Acids		
Collagen Hydrolysate	2.5 g	15.2 g
Acetylcysteine	80 mg	485 mg
Vitamins		
Vitamin A	375 µg (1,250 I.U.*)	2.3 mg (7,566 I.U.*)
Vitamin C	475 mg	2.9 g
Vitamin E (TE**) (incl. beta-carotene, lutein, lycopene, etc.)	70 mg	424 mg
Vitamin B_1 (Thiamin)	4 mg	24 mg
Vitamin B_2 (Riboflavin)	5 mg	30 mg
Nicotinamide	30 mg	182 mg
Vitamin B_6	5 mg	30 mg
Vitamin B_{12}	9 µg	55 µg
Vitamin K_1	60 µg	364 µg
Vitamin D_3	7.5 µg (300 I.U.*)	45 µg (1,816 I.U.*)
Folic Acid	400 µg	2.4 mg
Pantothenic Acid	18 mg	109 mg
Biotin	150 µg	909 µg
Minerals and Trace Elements		
Calcium	200 mg	1.2 g
Zinc	10 mg	61 mg
Selenium	50 µg	303 µg
Manganese	2 mg	12 mg
Copper	1,000 µg	6 mg
Molybdenum	50 µg	303 µg
Phytonutrients		
Citrus Bioflavonoids (mg)	50 mg	303 mg
Mixed Carotenoids (mg) (incl. beta-carotene, lutein, lycopene, etc.)	3 mg	18 mg
Essential Fatty Acids		
Fish Oil, including:	1.1 g	6.7 g
Eicosapentaenoic Acid (EPA)	500 mg	3 g
Docosahexaenoic Acid (DHA)	167 mg	1 g
Energy	259 kJ (61.6 kcal)	1,567 kJ (373 kcal)
Proteins	2.8 g	17 g
Carbohydrates	8.5 g	51 g
Fat	1.1 g	6.9 g

* International Units ** Tocopherol Equivalent

Against this background, a multicenter observational study (post-marketing surveillance) was performed to examine to what extent a clinical benefit can be observed in patients with knee osteoarthritis resulting from the controlled intake of a dietary food for special medical purposes that consists of a balanced combination of micronutrients and chondroprotective substances.

Material and methods

Study product

The dietary food for special medical purposes (Orthomol® Arthro plus) tested in this trial is a combination of 1,100 mg glucosamine sulphate, 400 mg chondroitin sulphate, 50 mg hyaluronic acid, 2.5 g collagen hydrolysate, 1.1 g fish oil (equaling 500 mg eicosapentaenoic acid and 167 mg docosahexaenoic acid) and antioxidants as well as other micronutrients in the daily amount to be taken (Table I). According to the manufacturer's instructions, the patients were advised by the attending doctors to take an oral daily serving of Orthomol® Arthro plus consisting of a bag of granulate and two capsules. Thus, the daily nutrient dosage amounted to the quantities shown in Table I.

Patient cohort

646 patients with knee joint osteoarthritis were recruited for the multicenter observational study. Only the patients who had been available for the complete documentation of all study parameters mentioned below and for the full period of observation were included in the final evaluation (n = 450). Based on the classification system developed by Kellgren and Lawrence (14), the patients were allocated to one of the osteoarthritis stages I – IV depending on the severity of the knee osteoarthritis (Table II).

Table 2: Kellgren & Lawrence classification of osteoarthritis (1957)

Stages	Characteristics
I – Onset of osteoarthritis	• Mild subchondral sclerosis • No osteophytes • No narrowing of joint space
II – Mild osteoarthritis	• Mild narrowing of joint space • Onset of osteophyte formation
III – Moderate osteoarthritis	• Narrowing of joint space • Significant osteophytes • Uneven joint surface
IIV – Severe osteoarthritis	• Significant narrowing of joint space • Deformation of bone ends

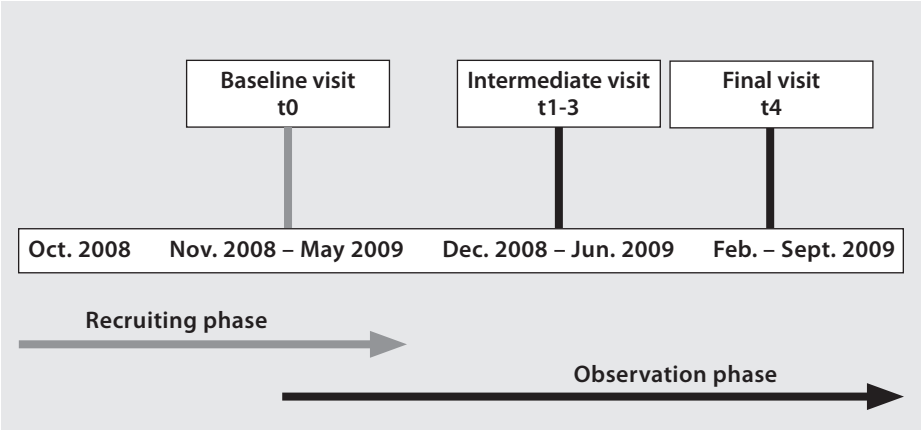

Fig. 1: Schedule of the multicenter observational study

Patients were recruited by 216 orthopedic specialists all over Germany. The post-marketing surveillance started in November 2008 and extended over a period of eleven months (Fig. 1). The observation period per patient was four months.

Study parameters

The primary study parameter of the non-interventional study was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC Global Index) developed in the Anglo-American world. This is a patient questionnaire of proven practical value that has also been available to, and evaluated and used by, the German-speaking area since 1996 (15). With the WOMAC Global Index both pain intensity and joint stiffness as well as physical activity can be recorded with valid results. For this purpose the patient must answer a total of 24 questions on a numerical scale (0-10). The WOMAC global score is then the computed mean value resulting from the three individual parts of the scale (15). Following the target parameters of the GAIT study by Clegg et al. (13), the proportion of the patients showing a reduction in the WOMAC pain score by ≥ 20 % was calculated as the primary parameter. In addition, the quality of life, the consumption of analgesics and the type and frequency of adjuvant therapies (physiotherapy, physical treatments, acupuncture and other forms of treatment) were recorded by means of a questionnaire. The target parameters mentioned were recorded at the beginning (t0) of the observation period and thereafter every 2 months until the end of the study period. The WOMAC Index was recorded monthly.

Table 3: Demographic and anthropometric characteristics of the patient cohort

	Mean value ± Standard deviation	1st quartile	Median	3rd quartile
Age (ys)	58.7 ± 13.7	49.0	59.0	70.0
Weight (kg)	80.5 ± 15.0	70.0	79.0	90.0
Body height (cm)	172.1 ± 8.4	166.0	172.0	178.0
Body Mass Index (kg/m²)	27.1 ± 4.4	24.2	26.4	29.2

Statistical methods

A statistics program (SAS 9.1.3 Service Pack 4) was used for the biometric data evaluation. The computed parameters of the descriptive statistics comprise the mean value, standard deviation, median and first and third quartile. The Wilcoxon signed-rank test for paired samples was used for the analysis of the WOMAC global, pain and stiffness scores. The analgesics consumption was evaluated by means of the McNemar test because a dichotomic characteristic is studied in a paired sample. The α-level for the significance test was fixed at 0.05 for the examination of the zero hypothesis (no difference between t0 and t4).

Results

Demographic and anthropometric characterization of the patient cohort

Based on the participation criteria, 450 of the 646 recruited individuals could be included in the trial. The collected data on age, body height and weight and the calculated Body Mass Index (BMI) are presented in Table III.

On the basis of this cohort, n = 421 subjects could be allocated to one of the osteoarthritis stages I-IV (stage I: 17.6 % [n = 79]; stage II: 33.6 % [n = 151]; stage III: 36.4 % [n = 164]; stage IV: 6 % [n = 27]). 6.4 % of the subjects (n = 29) could not be allocated to any of the four osteoarthritis stages. In the majority of patients (62.8 %; n = 279) the osteoarthritic degeneration process was not limited to the knee joint to be examined, but 27.6 % (n = 77) had hip osteoarthritis at the same time, 38.7 % (n = 108) had osteoarthritis of the spinal column, and 15.8 % (n = 44) had osteoarthritic changes of the hand and finger joints.

Effect on symptom reduction (WOMAC global score)

As Fig. 2 shows, a continuous reduction in the WOMAC global score was found over the 4-month period of observation. Based on its median and its arithmetic mean, a significant symptom reduction of 52.9 % and 40.5 % ($p < 0.0001$) occurred over the four months (t0 vs t4). As the subgroup analysis of n = 421 subjects indicates, patients in all osteoarthritis stages benefited from a dietary treatment with Orthomol® Arthro plus. On the basis of the arithmetic mean at t0 and t4 of the study, the WOMAC global score dropped by 52 % in patients of osteoarthritis stage I ($p < 0.0001$). The symptom reduction (WOMAC global score) for patients in stages II, III and IV was 31.2 to 44.4 % (t0 vs t4 $p < 0.0001$); the comparison of the medians (36.0 to 51.6 % reduction in the WOMAC global score between t0 and t4, $p < 0.0001$; Fig. 3) produced similar findings.

Effect on joint pain

In the course of the non-interventional observational study, the number of patients reporting a reduction in pain symptoms rose continuously during intake of the study product Orthomol® Arthro plus. In the first month about a third (32.7 %; n = 147) of the patients already felt an alleviation of pain of 20 % and more; in the second month this had even increased to as many as two thirds (57.8 %; n = 260) (Fig. 4).

At the same time a reduction in the pain intensity was achieved during the observation period. After four months of taking Orthomol® Arthro plus, 77.3 %

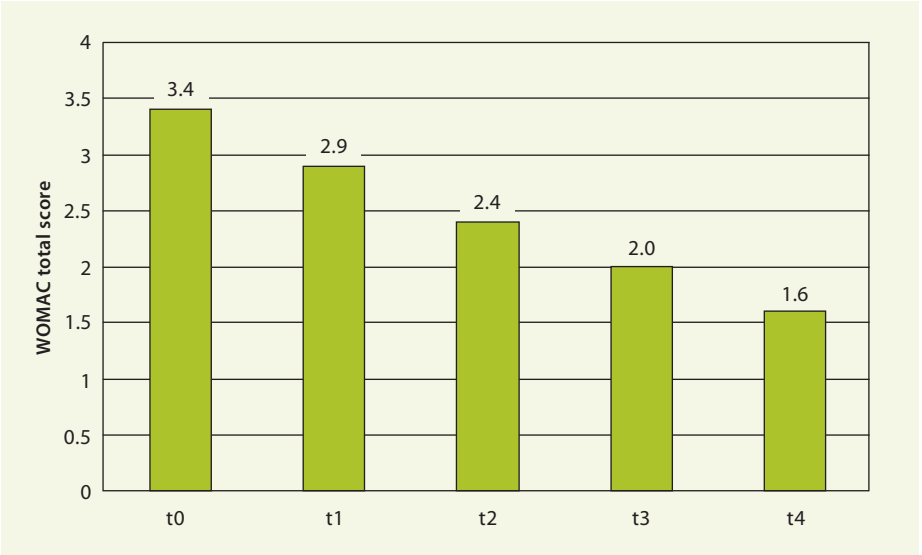

Fig. 2: Symptom reduction: medians of WOMAC total score at t0 to t4 (t0 vs t4 $p < 0.0001$; n = 450)

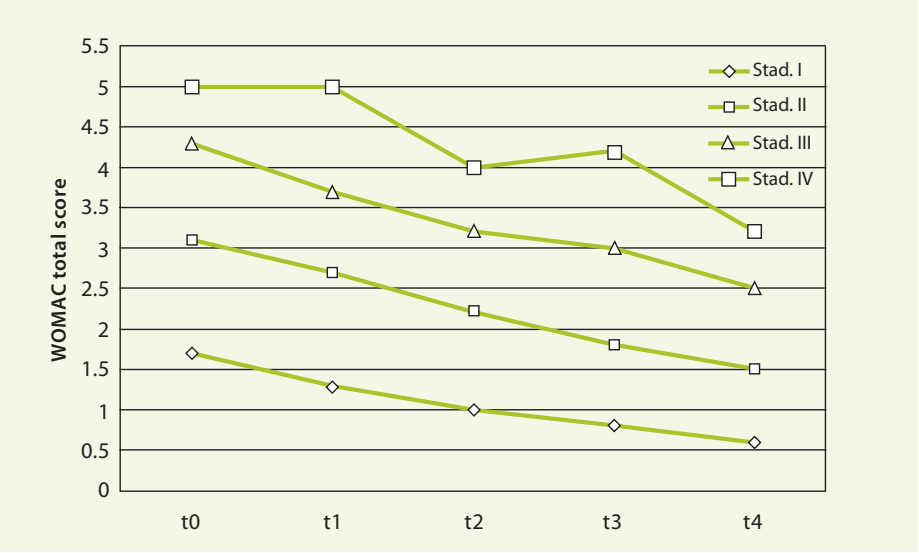

Fig. 3: Change in WOMAC total score (symptom reduction) over four months (t0 to t4) related to stages of osteoarthritis (median t0 vs t4 $p < 0.0001$; n = 421)

Fig. 4: Proportion of patients (all stages of osteoarthritis) who experienced pain reduction of ≥20% related to duration of study product use (n = 450)

(n = 348) of the patients experienced a pain reduction of 20 % and more, with 60 % (n = 270) of the patients the pain was even reduced by at least 40 %, and with almost one out of every three (38.4 %; n = 173) by at least 60 % (Fig. 5). As the comparison of mean values shows, the pain reduction was 8.9% after one month and 45.3 % after four months ($p < 0.0001$ at t0 vs t4). With a pain reduction of 7.7 % at t1 and 50.0 % at t4, a similar picture develops when the medians are compared.

Effect on joint stiffness

Besides the impact of the study product on pain intensity, its effect on joint stiffness was also investigated. Here too, a continuous and marked improvement in symptoms was found during the observation period. Thus, the mean value comparison between t0 and t4 showed that joint stiffness improved by 37.5 %; a similar result can be reported for the medians (reduction by 56.4 % between t0 and t4, $p < 0.0001$; Fig. 6).

Effect on quality of life

The symptom reduction also had an influence on the quality of life. 72 % of the patients who had complained about an impairment in their quality of life at the beginning of the observational study (n = 429), reported an improvement in their quality of life by the end. As a closer examination and analysis of the data shows, in particular the number of those patients who had felt a severe or very severe impairment in their quality of life could be effectively reduced (Fig. 7).

Effect on analgesics consumption and supportive therapy

An additional beneficial effect of the dietary therapy was that fewer patients required analgesics. Whereas at the start of the trial 44.9 % (n = 202) of the 450 patients took analgesics, this number had dropped to only 27.3 % (n = 123; $p < 0.0001$) four months later; Fig. 8). Moreover, an analysis of the group that had provided information about their analgesics consumption showed that 44.3 % could reduce the medication dose. Likewise, adjuvant measures were not required to the same extent as before the period of observation (Fig. 9). This benefit was particularly pronounced for physiotherapy: at the start of the trial (t0) 39.3 % (n = 177) of the patients reported a need for physiotherapeutic measures and at the end of the four months (t4) the figure had declined to 17.1 % (n = 77).

Discussion

Alleviation of pain, improvement of function, suppression of inflammation and a slower disease progression are

the principal aims of osteoarthritis treatment. Primarily symptom-oriented treatment procedures are included in the therapy, especially the application of anti-inflammatory and analgesic medication. However, the range of adverse events associated with the widely used non-steroidal anti-inflammatory drugs (NSAIDs) and corticoids often makes successful treatment difficult. Against this background, it is only logical to search for alternative forms of treatment that have a causative impact on the disease process and/or allow a reduction in medication. Nutritional medicine offers a number of appropriate measures with the possibility of supplementing conservative therapy in a useful and effective way. Therefore, dietary therapy is to be seen as an integral part of modern osteoarthritis treatment (3). The use of chondroprotective cartilage nutrients is of particular interest in this context. Besides glucosamine sulphate, chondroitin sulphate and collagen hydrolysate, specific micronutrients, such as vitamins, trace elements and long-chain omega-3 fatty acids are of importance (2). Their specific and balanced combination will produce mutually supplementing and enhancing effects from the chondroanabolic, antioxidant and anti-inflammatory characteristics of the individual substances. This was the basis for the development of Orthomol® Arthro plus, a dietary food for special medical purposes.

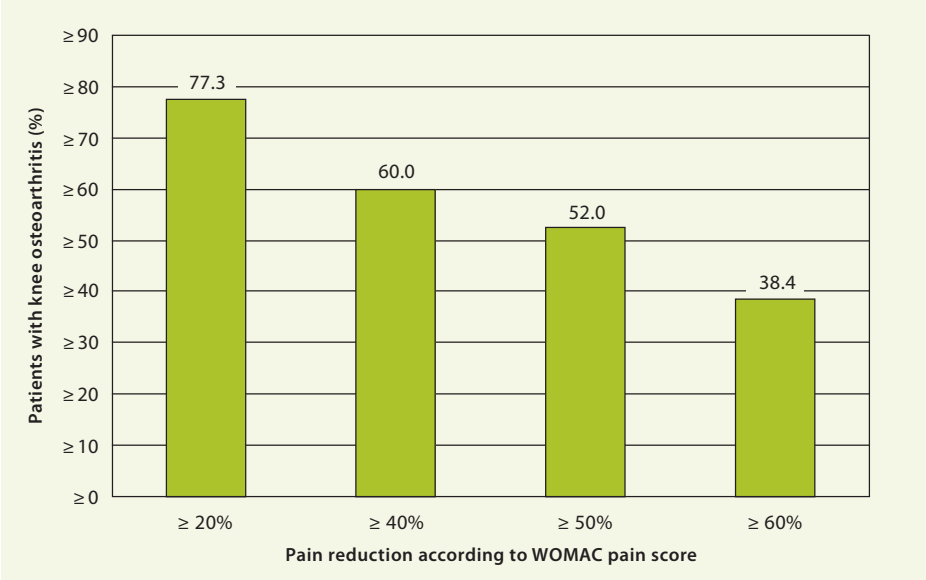

Fig. 5: Proportion of patients who experienced pain reduction of ≥20%, ≥40%, or ≥60% after four months of treatment with Orthomol® Arthro plus (n = 450)

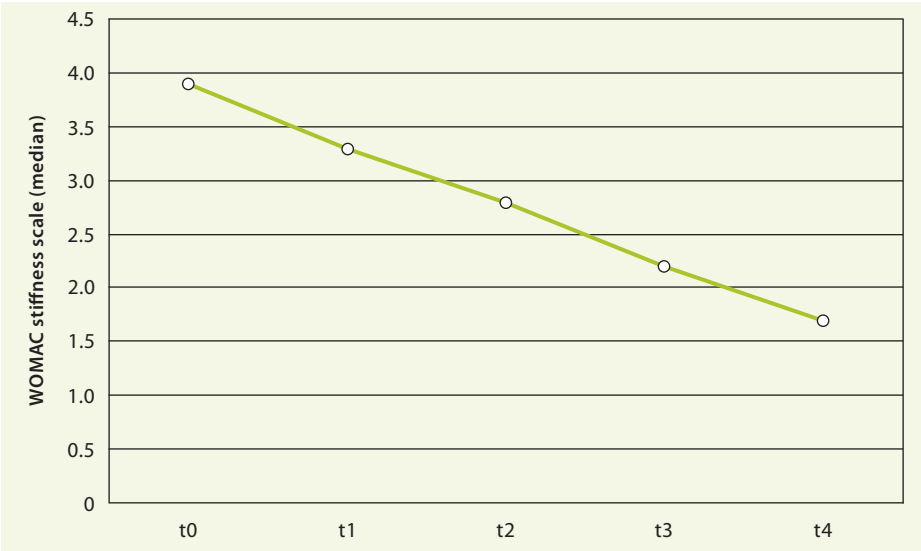

Fig. 6: Reduction in stiffness during the observation period (median t0 vs t4 $p < 0.0001$; n = 450)

The aim of the study was to investigate under practical circumstances the extent to which this dietary food for special medical purposes was associated with a clinical benefit for osteoarthritis patients. And in actual fact, the dietary treatment with Orthomol® Arthro plus alleviated symptoms and also led to a marked reduction in the medication dosage and an improvement in the patients' quality of life in the course of the multicenter observational study. It is important to note in this context that these positive clinical results demonstrated a clear time-effect relation: the longer the study product was taken, the greater the benefit to the patient. Placebo-controlled double-blind trials also underline the necessity of treating the patients for a sufficiently long period of time with the chondroprotective substances that are contained in the dietary food for special medical purposes studied. By way of example, reference is made here to the study of Uebelhart et al. (10) including 84 osteoarthritis patients (n = 41 in the placebo and n = 43 in the verum group); those in the verum group received 800 mg of chondroitin sulphate daily for a period of 12 months. As the evaluation of the data showed, the symptoms improved continuously in the course of the treatment period with the maximum clinical effect being reached not before at least nine months (10).

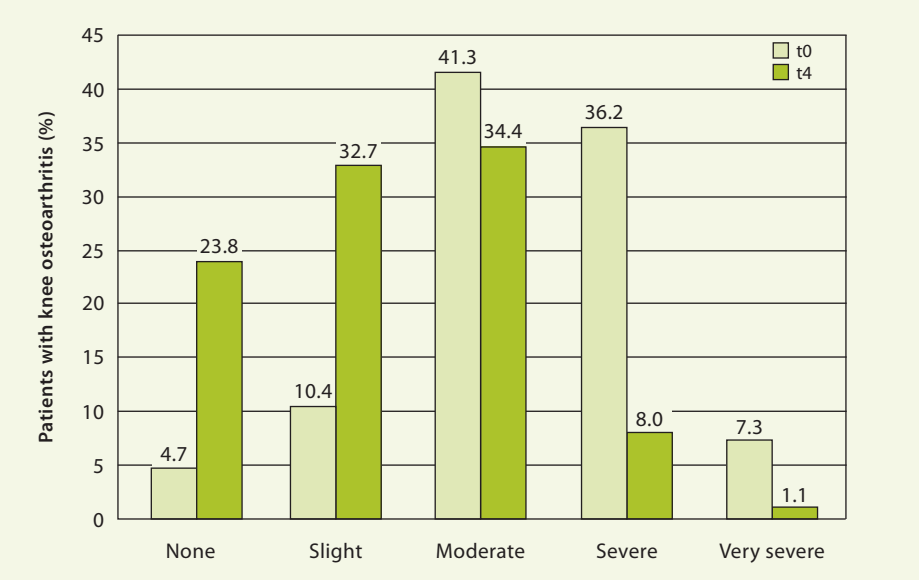

Fig. 7: Change in the number of patients who experienced a slight, moderate, severe or very severe impairment in their quality of life (t0 vs t4; n = 450)

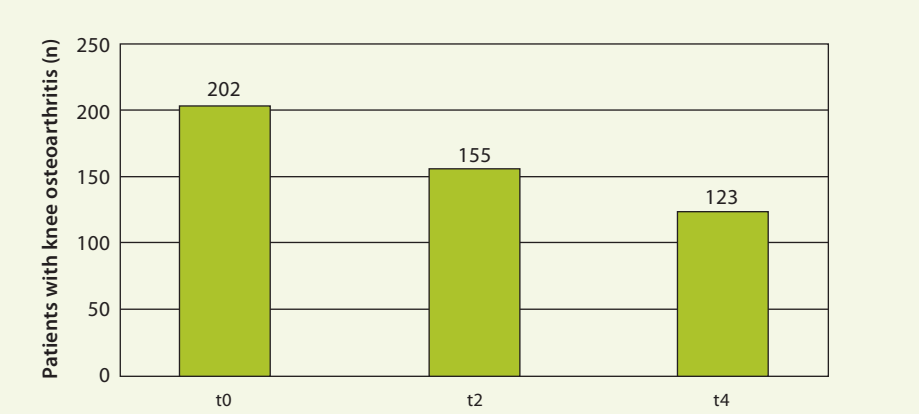

Fig. 8: Change in the number of patients who needed analgesics during the observation period (t0 to t4; n = 450)

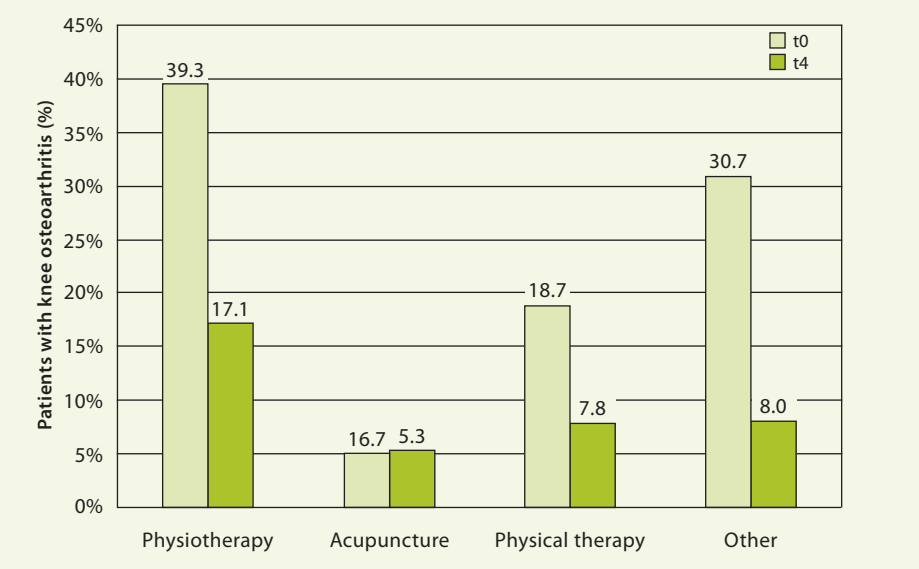

Fig. 9: Change in the number of patients who had used physical/physiotherapeutic and other supportive therapies in the course of the study (t0 to t4) (n = 450)

Besides the period of intervention, the combination of the nutrients included in the study product also seems to be important for the clinical benefit. The fact that chondroprotective substances are obviously able to develop synergies is suggested, for example, by the subgroup analysis in the GAIT study by Clegg et al. (13), which shows that the combination of glucosamine and chondroitin was superior to giving the patients each substance separately.

Against this background and in view of the fact that there are other micronutrients which are also important for the bone and cartilage metabolism, the beneficial clinical effect of the dietary food for special medical purposes seems to be mainly due to its particular composition, as the substances contained in the study product offer the chance of influencing the disease at different levels. Thus, the omega-3 fatty acids contained in Orthomol® Arthro plus slow down the inflammatory osteoarthritic process by antagonizing the impact of the proinflammatory arachidonic acid, inhibiting chondro-catabolic enzymes, such as aggrecanases and collagenases, and thus inhibiting the collagen degradation in the chondrocytes (16).

Moreover, various compounds contained in the dietary food for special medical purposes have an antioxidant effect, among them vitamins C and E, various carotenoids and bioflavonoids as well as the trace elements zinc, selenium and copper. These substances act as radical scavengers and as such are involved in the elimination of free oxygen radicals, e.g. superoxide anions and hydroxyl radicals which have a toxic effect on chondrocytes. The latter are formed in abnormally great numbers in osteoar-

thritis patients and are a causative factor contributing to cartilage destruction. Their chondrocatabolic effect is due, among other things, to their potential to activate cartilage-degrading enzymes and cause oxidative damage to the cartilage matrix (17, 18). Antioxidant compounds counteract such processes by activating the body's own antioxidant system. It could be demonstrated that vitamin E can significantly alleviate symptoms such as pain at rest, upon pressure and movement in patients suffering from osteoarthritis (19). The important factor is the combined administration of vitamins C and E, as vitamin E will oxidize itself when capturing free oxygen radicals and can only be regenerated by vitamin C (20).

Other micronutrients needed by the bones and cartilage are calcium and vitamins C, B_6, K_1 and D_3 (2, 3). All these micronutrients are contained in the study product and make a useful contribution to the treatment of osteoarthritis on the basis of nutritional medicine. In conclusion, another clinically interesting finding shall be mentioned in this context, i.e. the fact that in 75 % of the patients other osteoarthritic joints, such as those of the spinal column, hip and finger joints, also experienced an improvement or even absence of symptoms during intake of the dietary food for special medical purposes. This finding should be further investigated in greater detail in subsequent studies.

In summary, the dietary therapy with chondroprotective substances and micronutrients makes a valuable contribution to modern osteoarthritis treatment. In fact, the Orthomol® Arthro plus dietary food for special medical purposes provides a specific nutrient composition which, if taken according to a controlled regimen, is of clinical benefit to patients suffering from osteoarthritis. As the present observational study shows, the symptoms of such patients are alleviated and their quality of life improves during intake of the study product. The reduced need for analgesics stated is also of clinical interest.

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