Results of a Postmarketing Surveillance Study of Collagen Hydrolysate CH-Alpha®

Klaus Flechsenhar (1), Dietmar Alf (2)

(1)
Dr. Klaus Flechsenhar, Senior Manager Medical Affairs, Research & Development, GELITA AG, Gammelsbacherstr. 2, 69412 Eberbach, Germany
(2)
Dr. Dietmar Alf, Facharzt für Sport- und Leistungsmedizin (Sports Medicine Specialist), Olympiastützpunkt Rhein-Ruhr, Wittekindstr. 62, 45131 Essen, Germany

1. Zusammenfassung:

Am Olympiastützpunkt Rhein-Ruhr in Essen wurde an 100 Sportlern eine Anwendungsbeobachtung durchgeführt. Das Einschlußkriterium, welches die Probanden zur Teilnahme an dem Projekt zu erfüllen hatten, waren schmerzhafte Veränderungen der Extremitätengelenke aufgrund sportlicher Belastungen. Die Sportler, die zwischen 15 und 80 Jahren alt waren, nahmen über 12 Wochen hinweg täglich 10 Gramm Kollagen-Hydrolysat CH-Alpha® zu sich. Am Ende der Anwendungsbeobachtung, d.h. nach 12 Wochen Einnahme Kollagen-Hydrolysat CH-Alpha®, hatten sich bei sehr guter Verträglichkeit des Nahrungsergänzungsmittels die Parameter „Funktionseinschränkung“, „Bewegungsschmerz“, „Treppensteigen“ und „Überkopfarbeiten“ deutlich gebessert.
Schlüsselwörter :
Anwendungsbeobachtung, Kollagen-Hydrolysat CH-Alpha®, sportliche Aktivität, Arthralgien, Messung klinischer Parameter mit Hilfe der visuellen Analog-Skala

2. Summary :

At the Olympic Center Rhein-Ruhr in Essen a post-marketing-surveillance-study which included 100 athletes was carried out. The inclusion criterion that the participants had to fulfill was pain in the lower or upper extremities due to physical activity. The athletes whose age ranged between 15 and 80 years consumed a daily dosage of 10 grams of collagen hydrolysate CH-Alpha® for the duration of 12 weeks. At the end of the post-marketing-surveillance-study, i.e. after 12 weeks of oral administration of collagen hydrolysate CH-Alpha®, a good tolerance of the nutritional supplement was reported. Furthermore, clinical parameters that were determined like “restricted ability to move”, “pain related to exertion”, “pain when walking up the stairs” and “pain when manipulating objects with one´s hands above the head” were found to have significantly improved.
Key words :
Post-marketing-surveillance study, collagen hydrolysate CH-Alpha®, physical activity, arthralgias, determination of clinical parameters with the aid of a visual analogue scale

3. Introduction and Hypothesis:

Osteoarthritis (OA) is a degenerative joint disease (DJD) characterized by gradual destruction of articular cartilage. DJD also affects anatomically adjacent structures such as bone, joint capsules, tendons, and muscles. Often called "wear-and-tear arthritis" or "old person's arthritis," OA tends to get worse as a person gets older. This means that OA is more likely to interfere with an individuals's overall health with increasing age.

The health economic impact of OA is increasing as well. In Germany alone, annual expenditure arising from wear-and-tear arthritis is now estimated at € 10 billion.

Physicians who care for OA patients have several therapeutic options to choose from. Therapeutic objectives include reduction of pain, maintenance of joint mobility, prevention of periarticular complications such as acute inflammatory flares, and delay of progression of the overall degenerative process. The use of potent drugs is a pillar of OA management.

Glucosamine and chondroitin are building-blocks for the synthesis of proteoglycans. Nonsteroidal antiinflammatory drugs such as diclofenac or ibuprofen and acetaminophen (used for its analgesic activity) may provide significant relief of osteoarthritic pain. A glutathione precursor, S-adenosylmethionine (ademetionine) has both antiinflammatory activity and structure-modifying properties, and it may also increase chondrocytic glycosaminoglycan (GAG) synthesis. Intraarticular injection of glucocorticoids is typically used for pain relief, while intraarticular hyaluronic acid is used against a different pharmacologic or pathophysiologic background: A polysaccharide, hyaluronic acid can produce measurable changes in synovial fluid viscosity to improve joint mobility.

Nonpharmacologic treatments with significant potential to impact favorably on disease progression include therapeutic exercises to maintain joint mobility and functional training like isometric and isokinetic exercises to prevent further mobility restrictions.

A nutriceutical that may be useful in OA patients and has become increasingly important over the past few years, collagen hydrolysate is derived from collagenous materials such as porcine or bovine hide and bones. Collagen is a polymer with a molecular weight of 300,000 Da. Enzymatic hydrolysis, heat sterilization, and drying result in a product called collagen hydrolysate. Its average molecular weight is 3,300 Da; it does not form a gel; and it is soluble in cold water.

Having the same amino acid sequence as native collagen, collagen hydrolysate has long been considered by biochemists and clinical researchers to qualify as a potential building-block of cartilage or connective tissue in general.

Our knowledge of the effects of collagenous substances on joint health can, in fact, be traced back to the Middle Ages. Hildegard von Bingen (1098–1179; famous German mystic, theologian, essayist, philosopher, composer, and natural scientist) described a recipe that involves scalding and cooking calves' feet and eating all of the resulting dish, including the remnants of fatty tissues and hide. This remedy, Hildegard claimed, would make the stinging pain in joints and the stomach go away.

In modern times, research in this area has advanced so that therapeutic intuition and folk medicine beliefs have come to be supported by prospective, randomized, placebo-controlled clinical trials and laboratory studies meeting the criteria of evidence-based medicine.

The effect of collagen hydrolysate on DJD has been the subject of clinical research for over three decades. Krug (1), in 1979, published data on 193 patients with knee OA with tibial, femoral or retropatellar involvement, or with degenerative disk disease (DDD) of specific parts of the spine. Patients received collagen hydrolysate for 1 to 6 months and clearly benefited from this treatment. Interestingly, patients with DDD of the facets became all but free from pain.

Götz (2) treated 60 patients diagnosed with retropatellar OA with collagen hydrolysate for three months and documented a number of parameters including ability to climb stairs, soft tissue swelling, retropatellar crepitus, and knee effusion. Retropatellar crepitus (a sign typical of patellar chondropathy) was present in 58 patients at baseline, but disappeared in 47 of these after one month's treatment with collagen hydrolysate. Moreover, 52 patients experienced appreciable improvement in pain when climbing stairs.

Oberschelp (3), in 1985, published an open-label study of 154 patients with OA of the knee, hip, or lower spine randomized to one of three treatment groups: therapeutic exercises, therapeutic exercises plus collagen hydrolysate, or collagen hydrolysate alone. The duration of treatment was three months in all three groups. A pain assessment scale was used to quantify pain intensity at baseline and after three months' treatment. The pre-post differences were compared between the three treatment groups. Oberschelp found that the combined use of therapeutic exercises and collagen hydrolysate was as effective as collagen hydrolysate alone, and that collagen hydrolysate alone was better than therapeutic exercises alone.

Adam (4), a rheumatologist, was the first to have conducted, in the 1980s, a prospective, randomized, double-blind, placebo-controlled clinical trial meeting the criteria of good clinical practice (GCP) to explore the clinical effect of the nutriceutical collagen hydrolysate on DJD. Adam recruited 81 patients with OA of the knee or hip and used a complex cross-over design to compare four different nutritional supplements including collagen hydrolysate. Adam found that 81% of all patients taking collagen hydrolysate achieved significant pain reduction, but only 23% of placebo patients. Moreover, analgesic use was halved when using collagen hydrolysate.

Moskowitz (5) conducted a prospective, randomized, double-blind, placebo-controlled clinical trial of collagen hydrolysate between 1996 and 1998. Twenty sites in three countries (Germany, United Kingdom, United States) recruited a total of 389 patients with knee OA diagnosed in accordance with American College of Rheumatology (ACR) criteria. Patients were randomized to take either a placebo or 10 grams of collagen hydrolysate per day for 24 weeks. Primary outcome measures included the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain score, function score, and patient global assessment. Interestingly enough, the German subpopulation of 112 patients (7% dropout rate) derived statistically significant benefit from collagen hydrolysate in terms of pain reduction and functional improvement. The UK and US

subpopulations failed to reach the level of statistical significance. However, the dropout rates in those countries were unacceptably high at 37% and 42%, respectively.

In a laboratory study using HPLC, Oesser (6), in 1999, showed that collagen hydrolysate in molecularly intact form is absorbed across the mucosal barrier. Using ^{14}C-labeled collagen hydrolysate, Oesser, in another experimental design, showed that collagen hydrolysate absorbed across the intestinal wall, accumulates in cartilage. In 2003, Oesser (7) published more laboratory study findings demonstrating that incubation of a chondrocyte culture with collagen hydrolysate increases type II collagen synthesis by a factor of 2.5.

Laboratory evidence thus suggests that collagen hydrolysate can stimulate *de novo* synthesis of a complete extracellular matrix in cartilage.

The current state of collagen hydrolysate clinical research along with experimental findings explaining the mechanism of action of collagen hydrolysate at the molecular biology level are clearly focused on osteoarthritis. In other words, the clinical efficacy of collagen hydrolysate has been demonstrated in patients with an established diagnosis of OA. This means that the clinical evidence generated to date reflects a secondary prevention approach, but there are as yet no clinical data to support the use of collagen hydrolysate for primary OA prevention or in other types of joint disease.

Against this background, we set out to study the effect of Collagen Hydrolysate CH-Alpha® in a population of subjects who were not yet diagnosed with OA but had painful limb joint problems as a result of high-intensity athletic activity.

The objective of this postmarketing surveillance study was to determine whether oral use of Collagen Hydrolysate CH-Alpha® in athletically active individuals suffering from arthralgia induced by high intensity athletic activity, confers benefit in terms of improvement in pain, functional limitations, or inflammatory activity.

This study aimed to determine whether participating athletes' subjective well-being and objective findings, as assessed by the treating physician, change when taking collagen hydrolysate and, if so, whether these changes can be quantified by selected outcome measures.

4. Methods:

At Rhine-Ruhr Olympic Training Facilities, Essen, Germany, this postmarketing surveillance (PMS) study enrolled 100 athletes with painful extremity joint alterations.

Included were athletes of various ages and classes suffering with knee, hip or shoulder pain.
Excluded were all athletes who (a) were in the acute phase of a joint injury or inflammatory (joint) condition; (b) were taking glucosamine or chondroitin, that is, OA medications that were not classified as corticosteroids, nonsteroidal antiinflammatory drugs, or cyclooxygenase 2 inhibitors (COX-2 inhibitors)*; (c) were expected to need a

change in existing analgesic or antiinflammatory medications during the PMS study; or (d) who had interfering concomitant diseases.

Subjects took 10 g of Collagen Hydrolysate CH-Alpha® per day for 12 weeks. Subjects were interviewed and assessed before starting to take collagen hydrolysate (baseline visit), during treatment (interim visit at 4 to 6 weeks after the start of therapy), and at the end of therapy (final visit at 12 weeks).

As mentioned, the objective of this study was to determine whether a subject's situation would improve with collagen hydrolysate and, if so, to quantify that improvement.

This was achieved by determining both objective and subjective outcome measures. Objective parameters were assessed by physical examination by the treating physician, while subjective parameters were based on patient-reported outcomes.

At the baseline visit, demographic parameters including age, sex, height, and weight were recorded along with the duration of pain in the affected joint, concurrent treatments, current clinical findings, and patient assessment of symptoms.

At the interim visit, *i.e.,* at 4 to 6 weeks after starting to take collagen hydrolysate, subjects had their current clinical status assessed and rated their subjective well-being and freedom from pain compared with their previous treatment.

At the final visit, subjects again had their current clinical status assessed and rated their pain. Also recorded were the change in comedication use and an assessment of collagen hydrolysate in terms of tolerability and acceptance of taste.

Clinical status measures, as assessed by the treating physician, included pain at rest, pain on movement, functional limitations, and inflammatory activity. The intensity of these parameters was rated on a scale of 1 (no pain, limitation or activity) to 10 (severe pain, limitation or activity)).

Patient-assessed pain intensity related to pain while walking, pain when climbing stairs, pain while standing, and pain at night for subjects with hip or knee problems. For those with shoulder arthralgia, pain when climbing stairs was replaced with pain when lifting or carrying objects, and pain while standing was replaced with pain during overhead activities. The intensity of these parameters was also rated on a scale of 1 (no pain) to 10 (extreme pain).

5. Results:

Outcome measures were analyzed descriptively, separately for knee, hip and shoulder problems. The use of descriptive statistics for analysis is motivated by the fact that this study was a PMS study rather than a controlled clinical trial. This means that no differences versus a control group can be calculated for the outcome measures. The parameters captured in the questionnaires were described in terms of absolute and relative frequencies, means, and medians.

Demographic data such as age, height, and weight were described in terms of the mean and standard deviation.

This postmarketing surveillance study enrolled 100 subjects and 11 of these failed to return for the final visit and, therefore, would be considered dropouts in a formal clinical trial. One subject was not documented for diagnostic group assignment and, therefore, was also excluded from analysis. A total of 88 patients were thus available for analysis; 84 were completely documented.

Subjects' age ranged from 15 to 80 years, with a mean (± standard deviation) age of 41.5 ± 16.3 years.

Thirty-five of the 88 evaluable patients were women (39.8%), 51 men (58.0%), and 2 subjects (2.2%) had no gender specified.

Mean (± SD) body weight was 71.7 ± 8.3 kg, mean height 177.1 ± 9.0 cm, which gives a mean BMI of 22.8 ± 1.9 kg/m^2, suggesting an athletically very active patient population.

The mean duration of arthralgia in 79 subjects--9 subjects had no evaluable data--was 30.8 ± 27.4 months, median duration of pain being 24 months across all three diagnostic groups.

Of the 88 evaluable subjects, 51 had knee arthralgia (58.0%), 20 hip arthralgia (22.7%), and 17 shoulder arthralgia (19.3%).

To describe the changes in parameters during the PMS study, the case report forms (CRFs) were analyzed for frequencies of reported pain scores.

The 10-point rating scale used to describe dimensions pain at rest, pain on movement, functional limitations, and inflammatory activity, as well as pain while walking, when climbing stairs, at rest, while standing, and at night, is based on the principle of visual analog scales. VAS-determined parameters are ordinal data and, therefore, should be assessed by the geometric mean or median (that is, the score below/above which 50% of the cases in a score distribution fall).

Change in Pain at Rest:
Figure 1 shows the change in pain at rest during the postmarketing surveillance study.
In the 51 subjects with knee pain, the median pain-at-rest score was 2 at baseline, 2 at the interim visit, and again 2 at the final visit.

In the 20 subjects with hip pain, median pain at rest was 3 at all three visits. The 17 subjects with shoulder pain had median scores of 2 at baseline and the final visit, and of 1 at the interim visit.

Change in Pain on Movement:
Figure 2 depicts the change in pain on movement during the PMS study.
In the 51 subjects with knee arthralgia, the median pain-on-movement score was 5 at baseline, 4 at the interim visit, and 3 at the final visit.

In the 20 subjects with hip arthralgia, median pain on movement was 5 at baseline and the interim visit, and decreased to 4 at the final visit. The 17 subjects with shoulder arthralgia had a median score of 5 at baseline, 4 at the interim visit, and 3 at the final visit.

Change in Functional Limitations:
Figure 3 shows the overall change in functional limitations in the PMS subjects broken down by diagnostic groups.

In the subjects with knee arthralgia, the median functional limitations score was 3 at baseline and the interim visit, and 2 at the final visit. The subjects with hip arthralgia had a mean score of 4 at baseline, 3 at the interim visit, and 2 at the final visit. Shoulder pain subjects were enrolled with a mean functional limitations score of 5 and improved to 3 by the interim visit and 2 at the final visit.

Change in Inflammatory Activity:
Figure 4 shows the overall change in inflammatory activity during the PMS study.

Subjects with knee pain had a median inflammatory activity score of 2 at baseline, 1.5 at the interim visit, and 1 at the final visit. Those with hip problems had a median score of 1.5 at baseline, 2 at the interim visit, and 1 at the final visit. In the shoulder pain subjects, the median inflammatory activity score was 2 at baseline and 1 at both the interim and final visits.

Change in Pain While Walking:
Figure 5 depicts the change in pain-while-walking scores.

The 51 subjects with knee arthralgia were enrolled with a median score of 4 and improved to 3 at both the interim and final visits. The 20 hip pain subjects had a median score of 4 at baseline and the interim visit, and of 1 at the final visit. In the 17 subjects with shoulder problems, the median pain-while-walking score was 1 at all three visits.

Change in Pain When Climbing Stairs / Lifting or Carrying Objects:
Figure 6 shows the change in pain when climbing stairs for patients with knee or hip arthralgia or pain when lifting or carrying objects for subjects with shoulder pain.

The 51 subjects with knee problems had a median score of 6 at the baseline visit and of 4 at the interim and final visits.
Hip pain sufferers improved from a median score of 6 at baseline to 5 and 3 at the interim and final visits, respectively. The 17 subjects with shoulder problems had a baseline score of 4, improving to 3 at both the interim and final visits.

Change in Pain at Rest:
Figure 7 depicts the change in median pain-at-rest scores.
Subjects with knee problems had a median score of 3 when enrolled and of 2 at the interim and final visits. Those with hip arthralgia showed a median score of 4 at baseline and of 2 at both the interim and final visits. PMS study participants with shoulder arthralgia had a median pain-at-rest score of 2 at all visits.

Change in Pain While Standing or During Overhead Activities:
Figure 8 shows the change in pain while standing for patients with knee or hip arthralgia or pain during overhead activities for subjects with shoulder problems.

The 51 subjects with knee arthralgia had a median score of 2 at all three study visits. The 20 subjects with hip problems had a median score of 3.5 at baseline, 2.5 at the interim visit, and 4 at the final visit. The 17 patients with shoulder arthralgia were enrolled with a median score of 5, which decreased to 4 by the interim visit, and to 3 at the final visit.

Change in Pain at Night:
Figure 9 depicts the change in pain at night during the PMS study.
The 51 subjects with knee problems had median scores of 2 at the baseline and interim visits and of 1 at the final visit. Subjects with hip and shoulder problems had baseline, interim visit, and final visit scores of 2.5, 2, and 2, and of 2, 2, and 1, respectively.

At the start of the postmarketing surveillance study, 15 subjects with knee problems reported taking analgesics, 24 indicated taking nonsteroidal antiinflammatory drugs or COX-2 inhibitors, and one subject admitted to taking another comedication. At the end of the study, as few as 9 subjects with knee arthralgia were still taking analgesics, and 7 reported they were still on nonsteroidal antiinflammatory drugs or COX-2 inhibitors.

Among the patients with hip arthralgia, 10 were taking analgesics when enrolled, and 9 reported they were taking NSAIDs or COX-2 inhibitors at baseline. At the final visit, 2 patients with hip problems were still taking analgesics and 3 were still on NSAIDs or COX-2 inhibitors.
Among the subjects with shoulder arthralgia, 2 reported taking analgesics, 1 cortico-steroids, and 14 nonsteroidal antiinflammatory drugs or COX-2 inhibitors when enrolled. At the end of the PMS study, one patient each was still taking analgesics or cortico-steroids, and 3 were still on NSAIDs or COX-2 inhibitors at the final visit.

At the final visit, subjects were interviewed about the tolerability of Collagen Hydrolysate CH-Alpha® and the quality of this nutriceutical's taste. On a scale of 1 (excellent) to 10, 39 subjects (44.3%) gave the product's tolerability a score of 2. The taste of Collagen Hydrolysate CH-Alpha® received a score of 2 from 36 subjects (40.9%).

6. Discussion:

Previous clinical trials of Collagen Hydrolysate CH-Alpha® enrolled only patients with a clinical and radiologic diagnosis of osteoarthritis.

The present postmarketing surveillance study recruited patients who did not have a diagnosis of OA but rather had athletic activity-induced painful limb joint problems. While it might be argued that such "problems" do not qualify as a genuine diagnostic entity, there is no arguing that sports physicians frequently do see patients with athletic activity-induced arthralgia and are expected to offer treatments that work.

Subjects in this PMS study typically reported few symptoms captured by measures of pain at rest: The average baseline score reported for pain at rest and pain at night was as low as 2. This reflects the athletic nature of our patient population: Individuals with pronounced pain at rest have little inclination to engage in athletic activities.

On the other hand, subjects with hip or knee arthralgia had median baseline scores as high as 5 and 6 for parameters such as pain on movement and pain when climbing stairs, respectively.

These baseline scores demonstrate the intensity of those symptoms during athletic activity and that those subjects are motivated and willing to take a nutriceutical for pain relief and to boost their performance.

Figures 1-9 show that most PMS study participants improved on most outcome measures during the study, as evidenced by the overall "right shift" of the bar graphs. The bar graphs depict the changes observed between the baseline and final visits. In numerical terms, these figures reflect the pre-post difference of the geometric means or medians.

If collagen hydrolysate had been clinically ineffective in this patient population, all subjects would have remained at baseline (0) on all outcome measures. Interestingly, all bar charts show the overall shape of a right-shifted normal (Gaussian) distribution; however, a few patients experienced a left shift (worsened).

Closer inspection of Figure 2 (depicting the change in pain on movement) reveals that 68 subjects improved, 19 were unchanged or worsened, and 1 patient was incompletely documented for pain on movement. The ratio of 68 subjects whose pain on movement improved to the 87 completely documented study participants gives a value of 78.2%. In a 1991 cross-over study enrolling 81 patients, Adam (4) showed that 81% of study participants achieved significant pain reduction after taking collagen hydrolysate for 8 weeks.

These data suggest that, while a postmarketing surveillance study, by definition, does not include a control group, the results of this PMS study, conducted at Rhine-Ruhr Olympic Training Facilities, Essen, Germany, are consistent with the findings of Adam's prospective, randomized, placebo-controlled clinical trial.

Figure 6 shows similar results: 68 of the 86 completely documented subjects, or 79.1%, showed improvements in pain when climbing stairs (subjects with hip or knee arthralgia) or pain when lifting or carrying objects (subjects with shoulder arthralgia).

At a mean age of 41.5 years and a mean BMI of 22.8 kg/m^2, this study population is obviously a relatively young and physically active population. The observation that almost 80% of the subjects improved by up to 5 points on pain on movement and pain when climbing stairs (subjects with hip or knee arthralgia) or pain when lifting or carrying objects (subjects with shoulder arthralgia) during treatment with collagen hydrolysate, is almost identical to the clinical observations published by Krug (1), who concluded from his results that treatment with collagen hydrolysate is even more promising in younger patients.

Figure 4 (change in inflammatory activity) shows that the investigator found no improvement in inflammatory activity in 41 of the 86 completely documented subjects (47.7%). The scores of 31 of those 86 subjects (36.0%) improved by only one point. These results suggest that collagen hydrolysate has no effect on inflammatory activity. This observation is consistent with experimental data published by Oesser (6, 7) showing that collagen hydrolysate acts on chondrocytes to induce an increase in type II collagen and proteoglycan synthesis in the extracellular matrix, while having no effect on inflammatory factors.

The documentation of comedications taken by the subjects reveals that fewer medications tended to be taken in the course of the study. However, as only one in five study participants was taking analgesics, corticosteroids, nonsteroidal antiinflammatory drugs, or COX-2 inhibitors, it is difficult to draw scientifically sound conclusions from these data.

Results obtained in prospective, randomized, placebo-controlled clinical trials often tend to be hard to reproduce in day-to-day patient care outside the controlled setting of a formal trial. This is a major criticism leveled at uncompromising supporters of evidence-based medicine because this attitude all but ignores the merits of medical experience and expertise.

Against the background of these considerations, it is interesting to note that the effects of Collagen Hydrolysate CH-Alpha®, well documented in clinical trials in terms of pathophysiologic processes in OA, have been impressively reproduced, even in numerical terms, in a heterogeneous population under uncontrolled conditions.

The results of this postmarketing surveillance study conducted at Rhine-Ruhr Olympic Training Facilities, Essen, Germany, clearly confirm the favorable effects of Collagen Hydrolysate CH-Alpha® previously described in published clinical trials.

7. References:

(1)
Krug E : Zur unterstützenden Therapie bei Osteo- und Chondropathien. Zeitschrift für Erfahrungsheilkunde (1979), 11, 930 - 938

(2)
Götz B : Gut genährter Knorpel knirscht nicht mehr. Ärztliche Praxis, 92, (1982) 3130 – 3134

(3)
Oberschelp U : Individuelle Arthrosetherapie ist möglich. Therapiewoche 44, (1985) 5094 – 5097

(4)
Adam M : Welche Wirkung haben Gelatinepräparate ? Therapiewoche 41, (1991) 2456 – 2461

(5)
Moskowitz RW : Role of collagen hydrolyate in bone and joint disease. Seminars in Arthritis and Rheumatism, Vol. 30, No. 2 (October) 2000, 87 – 99

(6)
Oesser S, Adam M, Babel W, Seifert J : Oral administration of ^{14}C labelled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage of mice (C57/BL). Journal of Nutrition, 129, (1999) 1891 – 1895

(7)
Oesser S, Seifert J : Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen. Cell Tissue Research 311, (2003) 393 – 399

*Comment by the Authors:
Merck decided to withdraw the COX-2 inhibitor rofecoxib (Vioxx®) from the market because of an elevated incidence of cardiovascular events observed during a three-year colon adenoma prevention study at a time when the paper describing this postmarketing surveillance study was nearing completion. The present PMS study was thus completed at a time when clinicians were only beginning to consider a more cautious use of COX-2 inhibitors.

8. Figures

Figure 1
Overall Change in Pain at Rest

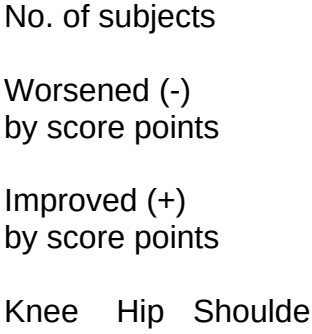

Figure 2
Overall Change in Pain on Movement

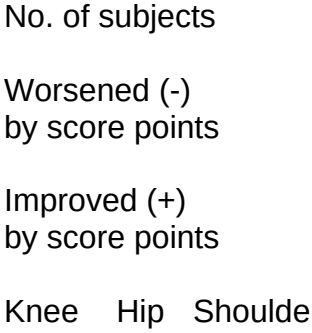

Figure 3
Overall Change in Functional Limitations

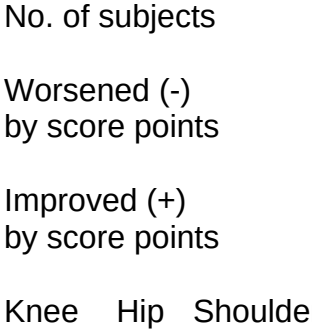

Figure 4
Overall Change in Inflammatory Activity

Figure 5
Overall Change in Pain While Walking

Figure 6
Overall Change in Pain When Climbing Stairs / Lifting or Carrying Objects

Figure 7
Overall Change in Pain at Rest

No. of subjects

Worsened (-)
by score points

Improved (+)
by score points

Knee Hip Shoulder

Figure 8
Overall Change in Pain While Standing or During Overhead Activities

No. of subjects

Worsened (-)
by score points

Improved (+)
by score points

Knee Hip Shoulder

Figure 9
Overall Change in Pain at Night

No. of subjects

Worsened (-)
by score points

Improved (+)
by score points

Knee Hip Shoulder