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ROLE OF COLLAGEN HYDROLYSATE IN CARTILAGE METABOLISM & REGENERATION

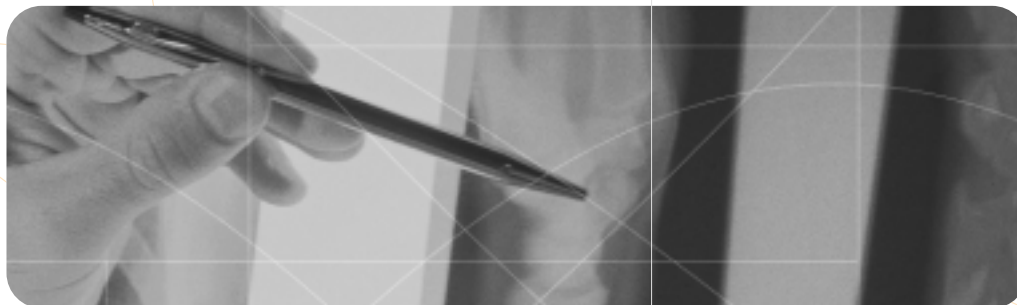
Satellite Symposium at the
World Congress on Osteoarthritis (OARSI)

ABSTRACTS



THE ROLE OF COLLAGEN HYDROLYSATE IN CARTILAGE METABOLISM & REGENERATION

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CURRICULUM VITAE



KRISTINE CLARK,
Ph.D., R.D., FACSM

Dr. Kristine Clark is the Director of Sports Nutrition for Penn State University's Athletic Dept. where she counsels more than 800 varsity athletes from 29 teams. In addition, she advises head coaches, team physicians, athletic trainers, strength and conditioning coaches, and athletic administration on policies regarding eating disorders, weight management, and supplement use among athletes. While most of Dr. Clark's time is devoted to athletics, she also holds a position of assistant professor in the Dept. of Nutrition at Penn State teaching a course titled, "Nutrition for Exercise and Health throughout the Lifecycle."

Dr. Clark was appointed to the Sports Medicine Advisory Board of the United States Olympic Committee in 1999. She began working as the nutritionist for the United States Women's Soccer Team in 1995 and continues as their nutrition consultant. In addition, she serves as the nutritionist for the United States Soccer Federation. Clark is the nutrition columnist for the Women's United Soccer Association website.

Dr. Clark holds a Ph.D. in Nutrition Science from Penn State University, a Masters degree in Health Education from the University of Wisconsin-LaCrosse, and a B.S. degree in Nutrition and Dietetics from Viterbo College, LaCrosse, WI. She is a registered dietitian, a Fellow in the American College of Sports Medicine, a Board of Trustees member of the ACSM, and is active in the Am. Dietetic Association.

*Kristine Clark, Ph.D., R.D., FACSM
Director of Sports Nutrition, Penn State Orthopedics
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// Currently, there is no medical cure for OA, only treatments to alleviate pain and symptoms. Accumulating evidence indicates that promising preventive measures such as nutrition may help slow down the onset of disease, improve symptoms and delay disease progression.

Information of joints due to aging, excess stress from physical activity or obesity may decrease mobility, effecting energy balance and further escalating weights.

The diet of an individual can therefore play a critical role in the prevention of disorders that can influence joint disease. Food choices that offer optimal levels of calcium, vitamin C, protein, phosphorus, and vitamin D contribute to normal formation of the extracellular matrix and articular cartilage required for healthy joint movement. In addition, weight management would help reduce any negative impact on the joints. In the United States alone, 64 percent of all adults are either overweight or obese. By the year 2008 obesity alone is predicted to reach 39 percent of all U.S. adults and 26 percent of children.

Though more clinical research is needed to determine the level of efficacy of various dietary supplements on improving measures of joint disease, research results on many have also shown promise. Ingredients such as omega-3 and omega-6 fatty acids, ginger and glucosamine with chondroitin sulfate are shown to relieve some degree of discomfort with joint stiffness, pain and inflammation. In addition, studies suggest that collagen hydrolysate, safe for use in food, may positively influence articular cartilage regeneration and support OA therapy. //

CURRICULUM VITAE



PROF JÜRGEN SEIFERT,
M.D.

Professor Seifert studied medicine at the University of Munich, Germany, and, having qualified as a Medical Assistant, worked in the Institute for Surgical Research at the university from 1967-1981. In 1974 he qualified as a university lecturer with his work on the enteral resorption of large molecular proteins and was awarded his professorship in 1979. In 1981 he was appointed Professor of Experimental Surgery at the Christian-Albrechts University in Kiel, Germany, and is currently Head of Surgical Research at the Hospital for General and Thoracic Surgery at the Kiel campus of the University Hospital of Schleswig-Holstein.

Apart from numerous studies on circulatory regulation and other clinical problems, Professor Seifert did much research work on the enteral resorption of foodstuffs, particularly proteins. He was able to show that proteins, even in large molecular form, could be resorbed whilst remaining biologically active. He followed up this work with studies where special emphasis was placed on the immunological aspects of the resorption-dependent influence of humoral defense mechanisms.

Professor Seifert has been awarded a number of prizes for his scientific work. He is a member of numerous national and international specialist societies and associations.

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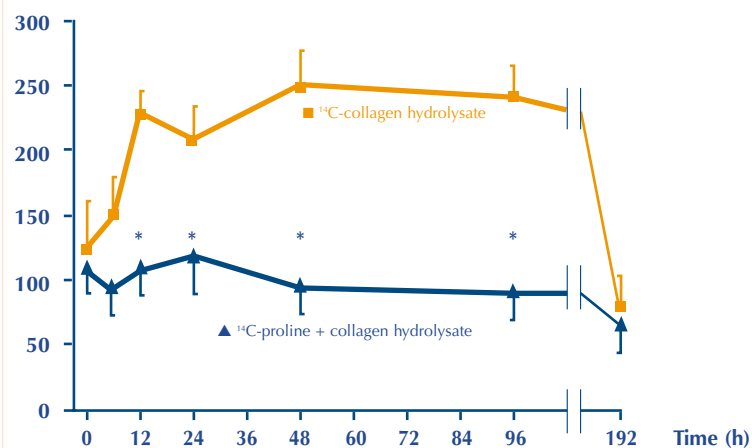
// Over the past several decades interest has expanded in the role of nutritional supplements as agents which may have a specific effect on disease pathophysiology. Collagen hydrolysate (CH), an enzymatically degraded collagen that received GRAS status by the FDA, has been used in the treatment of degenerative diseases of the musculo-skeletal system. In recent years a number of clinical studies have shown the benefits of orally administered CH on joint health. The therapeutic mechanisms, however, and in particular the intestinal absorption of CH, remain essentially unclear.

Therefore, the time course of CH absorption and its subsequent distribution in various tissues was investigated in a well-defined mouse (C57BL) model. Absorption of ¹⁴C-labeled CH was compared to control mice administered ¹⁴C-labeled proline following intragastric application. Plasma and tissue radioactivity was measured over 192 hours. Moreover, additional experiments were conducted to quantify the molecular weight distribution of the absorbed collagen fragments using SDS-electrophoresis and HPLC.

Experimental investigations have demonstrated that subsequent to rapid intestinal absorption of CH, measured radioactivity in cartilage was more than doubled compared to the control group, indicating a preferential and long lasting accumulation of CH derived fragments in cartilage tissue (FIG1).

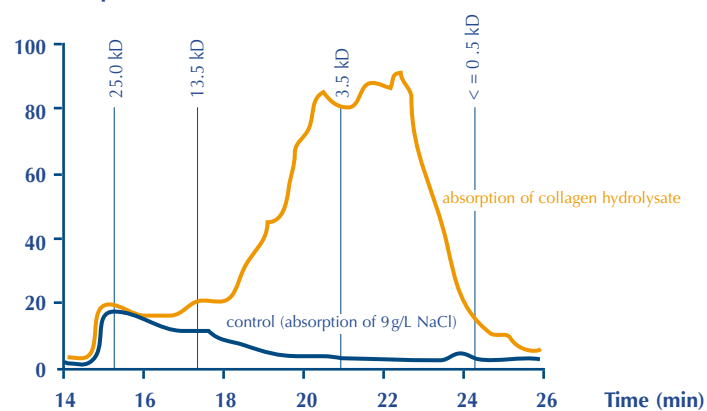
Furthermore absorption of CH in its high molecular form, with peptides up to 10 kDa, was detected following intestinal passage (FIG2).

Radioactivity (dpm/100mg cartilage)



Time course of radioactivity in cartilage of mice subsequent to absorption of orally administered ¹⁴C-labeled collagen hydrolysate and ¹⁴C-labeled proline in the control group. The mice received a standard dose of radioactivity of 580 Bq/g body weight and 10 mg collagen hydrolysate / g body weight. The results are presented as mean ± SD, n = 6. Asterisks indicate p < 0.05 significantly different from the control group.

UV-absorption (%)



GPC-HPLC chromatograms of the absorption medium from "mice gut sac" experiments 30 min subsequent to absorption of collagen hydrolysate and 9g/L NaCl solution in the control experiment.

Based on these results the observed beneficial effect of orally administered CH on osteoarthritis might be explained by the demonstrated accumulation of collagen fragments in cartilage tissue and the impact of these peptides on cartilage turnover. //

CURRICULUM VITAE



STEFFEN OESSER,
Ph.D.

As a Scientific Assistant at the Institute for Physiology of the University of Kiel, he initially concentrated on the areas of cell physiology and protein chemistry. Since 1993, Dr. Oesser has been active in medical research at the Schleswig-Holstein Hospital. Subsequent to his doctoral thesis on the influencing of chondrocyte metabolism, he has been principally involved in researching the pathophysiology of osteoarthritis and the development of new therapy possibilities for the treatment of degenerative disease of joint cartilage.

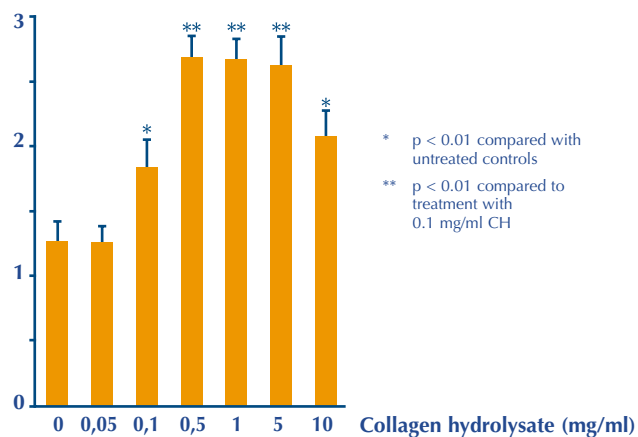
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// Consensus exists that the therapeutic goal of causal treatment of osteoarthritis can only occur by targeting chondrocyte metabolism to counteract the catabolic processes taking place in the joint cartilage. In principle, two therapeutic concepts are conceivable: inhibiting the degradation of the structural macromolecules in the extracellular matrix (ECM) or stimulating the biosynthesis of cartilage cells to compensate for pathologically caused degradation of the ECM.

Experimental investigations have demonstrated intestinal absorption of collagen hydrolysate (CH) in its high molecular form with peptides up to 10 kDa as well as a preferential accumulation of these CH derived fragments in cartilage tissue (Oesser et al. 1999).

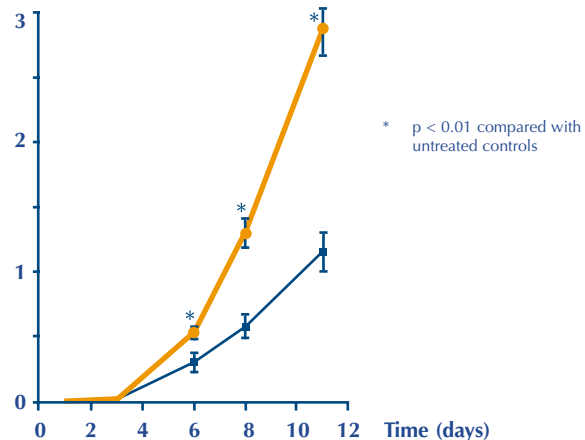
In recent studies the influence of CH on the metabolism of mature chondrocytes has been investigated in a primary cell culture model (Oesser and Seifert 2003). It was shown that the presence of CH in the culture medium led to a dose-dependent increase in type II collagen biosynthesis, whereas native collagen as well as collagen-free hydrolysates failed to stimulate the production of type II collagen in chondrocytes. These results clearly indicate a stimulatory effect of CH on the type II collagen biosynthesis of chondrocytes and suggest a possible mechanism for the regulation of collagen turnover in cartilage tissue.

Type II collagen ($\mu\text{g}/10^6$ chondrocytes)



Type II collagen secretion measured in the supernatants of 11-day-old bovine chondrocyte cultures after treatment with collagen hydrolysate. Data represent mean \pm SD of 6 chondrocyte preparations performed in duplicate.

Type II collagen ($\mu\text{g}/10^6$ chondrocytes)



Time course of type II collagen secretion into the supernatants of bovine chondrocytes cultured in basal medium (BM) or in medium supplemented with 0.5 mg/ml collagen hydrolysate (CH). Data represent mean \pm SD of 4 chondrocyte preparations performed in triplicate.

Moreover, utilizing immunocytochemical methods, it was demonstrated that in addition to an enhanced synthesis of type II collagen in chondrocytes treated with CH, the amount of pericellular aggrecan was significantly increased as well, indicating that the stimulated cells synthesize a complete extracellular matrix.

Based on these results CH might be of particular importance for the nutrition of cartilage tissue and might help to reduce degenerative alterations in the ECM. //

LITERATURE

Oesser et al. (1999): Oral administration of ^{14}C labeled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage of mice;

Journal of Nutrition 129: 1891-1895

Oesser and Seifert (2003): Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen;

Cell & Tissue Research 311: 393-399

CURRICULUM VITAE



PROF. H.-K. SELBMANN,
Dr. rer. biol. hum.,
Dipl.-Math.

In 1967 Prof Selbmann graduated in mathematics at the University of Stuttgart, Germany. After three years of serving as Head of the Scientific Computing Centre of the Du Pont Company at Neu-Isenburg he re-entered university and completed with a PhD graduation in Human Biology at the University of Ulm. In 1976, he took his Habitational Degree (postdoctoral lecture qualification) in Medical Statistics and Data Processing and worked as Professor and Deputy Director of the Institute of Medical Information Processing, Statistics and Biomathematics at the University of Munich from 1980 till 1984. Since 1984 he is Full Professor and Head of the Department of Medical Information Processing at the University of Tübingen. 1993 to 1995 he served as Dean of the Medical Faculty at the University of Tübingen and subsequently became for three years Speaker of the German University Professors for Medical Informatics, Biometry and Epidemiology.

Prof Selbmann was appointed to the Expert Council of the Concerted Action in Health Care of the Federal Republic of Germany (1988-1991) and to the Expert Council of Health Research of the Federal Minister of Education and Research (1990-2000). From 1992 on he was Chairman of this scientific committee. Since 1999 he officiates as Chairman of the Committee of Health Reporting of the Federal Republic of Germany.

In addition Prof Selbmann held office in several scientific societies and associations: he was President of the German Association of Medical Informatics, Biometry and Epidemiology (GMDS) (1985-1987) and Founding Chairman of the German Association of Quality Management in Health Care (GQMG) (1993-1997). Since 1993 he serves as Chairman of the Jury of the Golden Helix Award for Quality Management in Health Care.

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// In the age of evidence-based medicine, observations from experienced clinicians do not count, only good clinical studies do. A search for studies on the use of collagen hydrolysate in man has found 16 published and assessable studies. In 7 studies collagen hydrolysate was applied as monotherapy to patients suffering from osteoarthritis. These studies include about 850 patients. There were no serious adverse events reported in any of these studies.

The first of these 7 studies was conducted in the mid-eighties. The most recent, largest and methodically most extensive was a multinational, study dated from the years 1996-1998. In the last 20 years the requirements of good clinical studies, above all in the non-pharmaceutical field, have constantly increased.

Four studies were designed as double-blind, placebo controlled representing the state of the art in therapeutic research. They were examined more closely within the scope of a systematical review:

Study	Country	Number of Patients	Outcome	Characteristics
Adam 1991 and evaluation report	CSSR	52	Positive effect of PCH very likely	Cross over with 4 therapy groups over 16 months, reanalysis not possible.
Beuker and Rosenfeld 1996	D	92	Positive outcome is reported.	Inadequate evaluation, reanalysis not possible.
Moskowitz 1999	D, UK, USA	314	Effects significant only in D.	Cultural differences can have an influence.
Adam 2001 and biometric report	CSSR	44	Only Lequesne-index shows improvement.	Unpublished, study abandoned because of recruitment problems.

Two of these studies – Adam 1991 and Moskowitz 1999 – show statistically proven influences of collagen hydrolysate compareto placebo.

The study by Adam (1991) compared 4 treatments (collagen hydrolysate, non-hydrolyzed gelatin, non-hydrolyzed gelatin+glycine+CaHPO₄*2H₂O, egg albumin) in a cross-over design (2-month washout, 2-month treatment). All three gelatin preparations were significantly superior to egg albumin, though no significant difference between them, in reducing pain and the consumption of analgesics.

Unfortunately, collagen hydrolysate was not analyzed separately in the evaluation report and a reanalysis was not possible.

The multinational study (Moskowitz 1999) had a two arm (PCH 10g daily and placebo for 24 weeks) double-blind design. The 19 sites of the study were used as strata for the randomization permitting a separate analysis for all three countries. Paracetamol was allowed as an escape medication, the dosage was left to the patients. Differences in mean scores for the three primary efficacy variables between baseline and week 24 are presented in the following table:

	Total*	USA	UK	D**
Number of Patients				
PCH	161	86	18	57
Placebo	153	87	11	55
MEAN DIFFERENCES WEEK 24 AND BASELINE:				
WOMAC Pain Score				
PCH	63.9	64.4	36.1	71.9
Placebo	58.9	78.2	38.5	32.4
WOMAC Physical Function Score				
PCH	191.1	206.7	93.3	198.3
Placebo	167.1	240.9	127.3	58.3
Patient Global Evaluation				
PCH	0.4	0.4	-0.2	0.5
Placebo	0.3	0.3	0.4	0.2

* no significance; ** all variables significant at adjusted 5%

There were no statistically significant differences for the total study group in the three primary efficacy variables. However, all variables showed a significant improvement in the German part of the study. The different results between Germany and the other coun-

tries point to influences that could not be standardized in the multinational study, in spite of a common study protocol and only one involved CRO. Thus, between USA and Germany (in UK the number of patients was too small for a separate analysis) differences become apparent in:

	USA	D
Protocol violations	48%	17%
Drop out rate after 24 weeks	43%	18%
Paracetamol consumption>30 tab/week	45%	3%
Baseline values (WOMAC Pain Score)	253,3	217,9
Physician	Rheumatologists	Orthopedics

All these impact factors – especially the drop out rate with its underlying shortening of therapy duration and the consumption of analgesics with its impact on all three primary efficacy variables - are good reasons not to combine the results of the three countries in one analysis.

The two studies reported in more detail illustrate a distinct clinical impact of the collagen hydrolysate in patients suffering from osteoarthritis and confirm the results of recent experimental investigations. The other – methodically less extensive – studies point at least to the same direction although they do not have the same strength of evidence. //

LITERATURE

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Moskowitz RW (2000): *Role of Collagen Hydrolysate in Bone and Joint Disease; Semin Arthritis Rheum 30: 87-99*



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