Role of Collagen Hydrolysate in Bone and Joint Disease

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Objectives: **To review the current status of collagen hydrolysate in the treatment of osteoarthritis and osteoporosis.**

Methods: **Review of past and current literature relative to collagen hydrolysate metabolism, and assessment of clinical investigations of therapeutic trials in osteoarthritis and osteoporosis.**

Results: **Hydrolyzed gelatin products have long been used in pharmaceuticals and foods; these products are generally recognized as safe food products by regulatory agencies. Pharmaceutical-grade collagen hydrolysate (PCH) is obtained by hydrolysis of pharmaceutical gelatin. Clinical studies suggest that the ingestion of 10 g PCH daily reduces pain in patients with osteoarthritis of the knee or hip; blood concentration of hydroxyproline is increased. Clinical use is associated with minimal adverse effects, mainly gastrointestinal, characterized by fullness or unpleasant taste. In a multicenter, randomized, double-blind, placebo-controlled trial performed in clinics in the United States, United Kingdom, and Germany, results showed no statistically significant differences for the total study group (all sites) for differences of mean pain score for pain. There was, however, a significant treatment advantage of PCH over placebo in German sites. In addition, increased efficacy for PCH as compared to placebo was observed in the overall study population amongst patients with more severe symptomatology at study onset. Preferential accumulation of ^{14}C-labeled gelatin hydrolysate in cartilage as compared with administration of ^{14}C-labeled proline has been reported. This preferential uptake by cartilage suggests that PCH may have a salutary effect on cartilage metabolism. Given the important role for collagen in bone structure, the effect of PCH on bone metabolism in osteoporotic persons has been evaluated. Studies of the effects of calcitonin with and without a collagen hydrolysate-rich diet suggested that calcitonin plus PCH had a greater effect in inhibiting bone collagen breakdown than calcitonin alone, as characterized by a fall in levels of urinary pyridinoline cross-links. PCH appeared to have an additive effect relative to use of calcitonin alone.**

Conclusions: **Collagen hydrolysate is of interest as a therapeutic agent of potential utility in the treatment of osteoarthritis and osteoporosis. Its high level of safety makes it attractive as an agent for long-term use in these chronic disorders.**

INDEX WORDS: Osteoarthritis; osteoporosis; collagen hydrolysate; arthritis therapy; cartilage; bone.

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IMPROVED KNOWLEDGE about disease origins, pathophysiology, and clinical presentations has led to significant advances in the management of both osteoarthritis (OA) and osteoporosis, two of the most common musculoskeletal disorders. Advances in the treatment of OA include newer, safer medicines targeted toward symptomatic relief such as COX-2 selective inhibitors (1,2) and intra-articular hyaluronans (3-7). Further advances appear to be in the offing, with the development of medications directed toward disease modification, providing opportunity for disease retardation, stabilization, or reversal of structural changes. Tissue engineering, with opportunities for utilization of cells and matrix for tissue regeneration, adds additional excitement with the potential for comprehensive treatment of patients with joint degeneration. Similarly, a series of newly introduced medications provide opportunity for effective management of osteoporosis, with agents capable of both prevention and repair. Medications that include estrogenic hormone replacement, bisphosphonates, calcitonin, selective estrogen receptor agonists, fluorides, and parathormone derivatives provide opportunity for specific disease modification, when used in association with exercise, calcium, and vitamin D intake. Unfortunately, in both OA and osteoporosis, therapeutic responses are limited in many patients despite the availability of new agents and modalities, or by toxicity or intolerance reactions in individual patients. Accordingly, even though significant gains have been made in the management of OA and osteoporosis, there remains significant room for development of medications that provide even greater symptomatic relief with less overall toxicity, as well as the formulation of agents capable of disease modification with minimal risks.

Over the past several decades, interest has expanded in the role of nutritional supplements (Nutraceuticals) as both symptom-relieving agents and agents that may have a specific effect on disease pathophysiology and pathologic structural changes. Certain of these agents, such as glucosamine and chondroitin sulfate, have become extremely popular as health food supplements purported to be efficacious in the treatment of OA (8-14). A number of short-term studies with these agents suggest that they have efficacy equal to that of nonsteroidal anti-inflammatory agents in the symptomatic management of OA.

Similarly, clinical studies have suggested a role for collagen hydrolysate in the management of OA, based on the postulate that hydrolyzed collagen with its abundant amino acids plays a role in cartilage matrix synthesis (15-19). Gelatine products, which have been used as foods for a number of centuries, are attractive with respect to safety and overall lack of toxicity (20-22). Relief of OA pain in the knee or hip was noted in a study of patients receiving 10 g collagen hydrolysate daily over a 2-month period (15). Because collagen hydrolysate has not been shown to have a direct analgesic or anti-inflammatory effect, a direct effect on joint tissues has been hypothesized. Collagen (gelatine) also has been marketed as a supplement for the maintenance of normal bone integrity and as an agent in the treatment of brittle nails (23,24) and abnormalities in scalp hair (25,26).

Partially hydrolyzed collagen (gelatine) is derived from animal sources. It has been used as a food since at least early medieval times. The first known description of the beneficial effects of gelatin ingestion in humans is from 1175, when St Hildegard wrote that eating gelatin improved joint conditions by reducing pain (27). The first commercial manufacture of gelatin was in Holland around 1685. Today, US commercial production of gelatin exceeds 75 million pounds per year, and worldwide production exceeds 250,000 metric tons, of which more than 60% is consumed in various kinds of products by humans.

Hydrolyzed gelatin products have long been used in pharmaceuticals and foods in the United States and Europe. Gelatin and a broad range of hydrolyzed gelatin products of varying molecular weights are widely ingested as foods in the United States. All of these products have either been affirmed as generally recognized as safe (GRAS) food products or have been proposed as GRAS by the Food and Drug Administration (FDA) Center for Food Safety and Nutrition (20).

Collagen hydrolysate is manufactured from animal bones and hides. The material is homogenized and washed, and the bones are demineralized with dilute mineral acid. The resulting product, ossein, is practically pure collagen. After alkaline or acid processing, depending on whether the source is bovine or pig skin, respectively, the raw materials are extracted in several stages with warm water. During this process, the gelatin goes into solution. After concentration, gelation takes place during the cooling process. Advanced variants of gelatin in

the form of gelatin hydrolysate do not gel any further, giving it the advantage of being soluble in cold water.

Pharmaceutical grade collagen hydrolysate (PCH) is a soluble powder obtained by hydrolysis of pharmaceutical gelatin (USP XXII/NF XVIII) by use of an enzymatic process with an FDA-approved enzyme. There is a final sterilizing step before drying.

The average molecular weight of PCH ranges from 2,000 to 6,000 Daltons (2 to 6 kD). Its molecular weight is less than the molecular weight of gelatin yet more than the average molecular weight of peptones. Unlike gelatin, PCH does not bind significant amounts of water, but it is dispersable and emulsion-stabilizing.

Although it is frequently stated that proteins such as gelatin taken in oral form are enzymatically digested to their amino acid components in the intestinal tract, gelatin peptides are only digested to a certain degree within the gastrointestinal tract, with a proportion of intact high-molecular-weight proteins reaching the serum subsequent to passing through the intestinal wall at a level of approximately 10%. This percent absorption can be increased by combining the protein with a pepsin-inactivating reagent such as ethylenediaminetetra-acetic acid. In this way, an excess of 50% of the orally administered high-molecular-weight protein can be absorbed.

Collagen hydrolysate generally has been regarded as having a low biologic value. It does not contain all of the essential amino acids; tryptophan is not present, and cysteine only in small amounts. However, the protein value of gelatin may relate not only to its amino acid composition, but also to its combined effect with other nutritional proteins. In animal experiments, high-value protein carriers (casein with addition of methionine) can be replaced up to one third by gelatin without animal growth being significantly affected. It is also regarded as a valuable nutritional component because of its excellent digestibility.

The excellent digestibility of gelatin is of advantage within the framework of nutritional therapy. It is a pure protein that, because of its high water-binding capacity, can be used as a basis for low-calorie carbohydrates or low fat foods. The positive effect of the oral administration of gelatin on skin and organs attached to the skin has been observed for some time (23-27). These positive effects include improvement in nail quality (23,24); an effect on the properties of hair and hair growth (25,26); and, in veterinary studies, improvement in hair and hoof quality and growth.

Studies conducted with gelatin-containing combination preparations show good tolerance. Side effects include a sensation of unpleasant taste, a feeling of heaviness in the stomach, and a bloated feeling after oral administration. Occasional pyrosis and eructation are observed.

Acute, subacute, mutagenic, and teratogenic toxicity testing of gelatin, gelatin hydrolysates, and peptones derived from gelatin (including the enzyme used for proteolysis) have not indicated any health risk. As with other proteins from egg powder or casein, damaging effects are not found (investigated in animal trials) until the administration of this special type of protein is increased to over 50% of the total protein intake. However, this should not be problematic if the patient maintains balanced nutrition.

CLINICAL INVESTIGATIONS

Osteoarthritis

Adam (15) evaluated the effects of PCH on OA. Eighty-one patients with hip or knee OA were initially enrolled in a randomized, double-blind, cross-over trial comparing Gelita-Sol (Deutsche Gelatine-Fabriken Stoess AG [DGF Stoess] D-69402 Eberbach, Germany) gelatin, gelatin plus glycine plus $CaHPO4.2H_20$, and egg albumin. Gelita-Sol D differs from PCH only in that the starting material in the latter is pharmaceutical gelatin, whereas the Gelita-Sol D starting material is food-grade gelatin. However, the chemical and physical parameters of both products are identical. Gelatin used in other areas of the study was non-hydrolyzed. Twenty-nine patients discontinued treatment early. Six reported an uncomfortable heaviness in the stomach; eight refused to cross over their study medications because they believed they had improved significantly; and 15 left for nonspecified reasons. Accordingly, the data represent results of 52 completers.

Of the 52 patients with degenerative hip or knee disease, 31 had hip OA alone, 11 had knee OA alone, and 10 had involvement both of hip and knee. Bilateral hip involvement was seen in 31 patients; and bilateral knee involvement in four. Duration of disease of more than 5 years was

observed in over half the patients; symptoms had been present for less than 2 years in only 10% of study patients.

Patients were treated daily with 10 g of each product orally in tablet form (0.5 g each tablet) for four 60-day treatment periods in a random sequence, with a 2-month washout between each treatment. Pain was assessed using a three-stage qualitative scale that measured 13 aspects of pain. Fifty-two patients completed all four treatment periods, including 24 women and 28 men (mean age, 56 years). Throughout the study, patients were allowed to continue use of prior analgesics or anti-inflammatory agents, maintaining a stable dose throughout the study. All three gelatin preparations were significantly superior to egg albumin on reduction of pain from baseline; no statistically significant differences were noted between the other three treatment regimens. Side reactions included primarily "an uncomfortable heaviness in the stomach."

By the end of the test cycle with any of the gelatin-containing preparations, analgesic consumption was reduced significantly as compared with consumption before treatment, with the least effect noted after administration of the egg albumin. No radiologic changes were noted during the study period. Laboratory tests indicated no significant changes in erythrocyte sedimentation rate, liver function studies, or antibody titers to all three types of collagen.

The investigators suggested that gelatin may have a direct analgesic effect, or that the administration of gelatin-containing preparations provides a pool of amino acids in the body that significantly improves matrix structure.

Although the above study describes a salutary effect of gelatin on the pain of OA, variation in disease definition at time of inclusion in the study; inclusion both of hips and knees as study joints; use of a newly defined outcome measure; and a significant drop-out rate represent caveats in interpreting the results of the investigation. The consistency of results in the three arms using gelatin, as compared with the egg albumin placebo, however, supports a therapeutic effect of collagen hydrolysate in the treatment of OA pain.

In other studies (28), Gelita-Sol D, 10 g daily, was administered to over 100 patients for durations varying from 1 to 6 months. Subjects who received Gelita-Sol D had significantly higher mean levels of hydroxyproline, a major constituent of collagen in their blood, than those in the placebo group. Although these trials were open-labeled, and provide limited support of efficacy, they further show the safe use of PCH at a dose of 10 g daily.

In summary, evidence suggests that the ingestion of 10 g PCH daily reduces pain in patients with OA of the knee or hip. It is postulated that this beneficial effect is achieved by increasing the synthesis of collagen in joint and cartilage. Ingestion of 10 g PCH daily increased the blood concentration of hydroxyproline. Lack of significant adverse effects is seen in the widespread long-term use of hydrolyzed gelatin and gelatin as foods, nutritional supplements, and in pharmaceutical dosage capsules. Accordingly, if PCH could be demonstrated to have a significant efficacious effect on the pain of OA, its safety profile would make it attractive for use. Based on studies performed thus far, and the anecdotal suggestion that intake of collagen hydrolysate has been associated with relief of pain and increased function in patients with OA, a formal multicenter, randomized, double-blind, placebo-controlled trial was initiated, with results as follows (29):

REPORT OF A MULTINATIONAL STUDY

The primary objective of this study was to evaluate the effectiveness of PCH compared with placebo in decreasing OA knee pain. It was hypothesized that the administration of these metabolic substrates may stimulate chondrocytes to synthesize collagenous matrix and to provide symptomatic improvement in OA. It had been suggested that PCH at a dose of 10 g daily can reduce the pain of OA, and the extensive marketing history indicated that this dosage would be safe and well tolerated by patients.

PATIENTS AND METHODS

Study Design

Inclusion criteria included a diagnosis of primary (idiopathic) OA of the knee defined by American College of Rheumatology (ACR) criteria (30) in patients ages 45 through 80; with a pain rating of 30-90 mm (0-100 mm scale) of the study knee on the (Western Ontario MacMaster) WOMAC (31) pain component item "walking on a flat surface" and/or "descending and/or ascending stairs" at screening and baseline. Other characteristics included the presence

of at least mild, moderate or severe pain on global evaluation by the patient; presence of symptoms compatible with OA for at least one year and a Kellgren-Lawrence scale rating of two or three on x-ray. Exclusion criteria included recent arthroscopy of the study knee; intra-articular hyaluronic acid in the preceding nine months; or intra-articular injections of corticosteroids in the preceding three months.

The study was a multicenter, randomized, double-blind, placebo-controlled trial. Three hundred eighty-nine patients were randomized in 20 sites; six in the United States (US), three in the United Kingdom (UK), and 11 in Germany. Paracetamol (acetaminophen) tablets were given as the escape medication for pain throughout the study. Patients were randomly allocated to either 10 g PCH or placebo. Both preparations contained fructose filler. Double-blind treatment was performed for 24 weeks, followed by an 8-week posttreatment washout. Clinical assessments occurred at screening (visit 1), baseline (visit 2), weeks 2, 4, 8, 12, 16, 20, and 24 (visit 9), followed by assessments at week 28 (visit 10) and week 32 (visit 11) representing posttreatment follow-up.

Primary efficacy measures were the WOMAC pain dimension score (31), WOMAC physical function dimension score; and patient's global evaluation. Major secondary efficacy measures included the WOMAC stiffness dimension scale; pain after a 50-foot walk; presence or absence of effusion, and paracetamol usage. Safety was assessed at all visits.

Primary efficacy analysis was performed on an intent-to-treat (ITT) population; in addition, analyses based on completers, and on protocol nonviolators, were performed.

There were no statistically significant differences for the total study group between treatments in the ITT analysis for the differences of the mean score for pain between baseline and visit 9 (24 weeks) for the evaluation of Pain, Physical Function, or Patient Global Assessment (see Tables 1 and 2). The mean difference in pain from baseline

Table 1: Differences in Mean Score for WOMAC Pain, Physical Function, and Patient Global Assessments Between Baseline and Visit 9 (24 Weeks) by Country and Treatment Group, All Randomized Patients

	US	UK	Germany	Total
Treatment group—PCH				
Pain				
No.	99	21	67	187
Mean	65.4 ± 97	29.6 ± 101	68.2 ± 76	62.4 ± 91
Physical function				
No.	99	21	67	187
Mean	206.2 ± 329	88.8 ± 377	180.3 ± 236	183.7 ± 305
Patient global*				
No.	99	21	67	187
Mean	0.4 ± 0.8	−0.2 ± 0.9	0.5 ± 0.7	0.4 ± 0.8
Treatment group—placebo				
Pain				
No.	100	20	66	186
Mean	77.1 ± 95	40.5 ± 84	32.2 ± 64	57.2 ± 86
Physical function				
No.	100	20	66	186
Mean	232.6 ± 325	149.8 ± 262	59.7 ± 210	162.3 ± 293
Patient global				
No.	100	20	66	186
Mean	0.4 ± 0.8	0.4 ± 0.7	0.2 ± 0.6	0.3 ± 0.7

NOTE. Scores are the score differences from baseline visit to week 24 (visit 9).

* Global evaluation: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme.

Table 2: *P* Values of Primary Efficacy Variables at Visit 9 (24 Weeks) by Country (ITT Analysis)

	US	UK	Germany
Pain	.46	.85	.016
Physical function	.46	.75	.007
Patient global	.76	.15	.074

for PCH-treated patients at visit 9 was 62.4, whereas the mean difference for placebo was 57.2 (Table 1). Similarly, mean score differences from baseline between treatment and placebo groups for physical function (183.7 *v* 162.3) and for patient global evaluation (0.4 *v* 0.3) showed no differences. There was, however, a statistically significant treatment advantage of PCH over placebo for pain and physical function, and a trend to significance in patient global assessment in German sites (Table 2). When individual countries were examined, the drop-out rates differed. Approximately 42% of patients in the US sites and 37% in the UK sites withdrew from the study before completion; fewer than 7% of patients in Germany withdrew. No obvious explanation for differences in drop-out rates could be found.

In an effort to identify possible subsets of the patient population who might benefit from treatment with PCH, analyses were performed in the patient subsets including patients with baseline global assessment rated severe or extreme versus none, mild, or moderate; patients with baseline Visual Analog Scale pain score greater than 220 mm on the WOMAC pain scale; patients aged 65 years or older; male versus female; patients with baseline radiologic severity Kellgren-Lawrence, grade 2 versus 3; and patients who, on responder analysis, indicated at least a 20%, 30%, or 40% improvement in pain over baseline.

Statistically significant findings were unlikely to be observed in any of these subsets in the overall population because the sample sizes were significantly reduced, and therefore the probability of detecting a moderate difference was low. However, trends were sought that might suggest potential benefits of PCH over placebo in some of these subsets.

Among all subsets examined, one subset provided fairly consistent trends in favor of PCH (Table 3). This was the subset in which the patient baseline global assessment was rated either severe or extreme. This subset consisted of 92 patients (50 PCH and 42 placebo), with 70% women and 30% men. In this subset, PCH was uniformly numerically better than placebo in all three primary efficacy variables, not only at the end of the treatment (24 weeks), but also at weeks 28 and 32; this numeric improvement with PCH was seen in the overall population as well as in the combined US

Table 3: Differences in Adjusted Mean Scores for Pain, Physical Function, and Patient Global Responses Between Baseline and Visits 9, 10, and 11 (24, 28, 32 Weeks) for Patients With Baseline Patient Global Score Severe or Extreme (ITT Analysis)

	PCH US + UK (n = 18)	Placebo US + UK (n = 24)	PCH Germany (n = 32)	Placebo Germany (n = 18)	PCH All (n = 50)	Placebo All (n = 42)
Pain—9	62.7	36.8	63.8	18.1	62.2	28.1
Pain—10	70.3	34.4	70.4*	9.0	69.1†	22.2
Pain—11	52.9	27.1	62.0†	−1.8	58.1†	11.3
Phy fct 9	127.4	86.4	187.3*	−40.4	152.0†	23
Phy fct 10	151.9	90.1	207.3*	−86.9	173.6*	−0.3
Phy fct 11	102.9	79.2	184.4*	−69.4	141.0	2.9
Pat glob 9	0.7	0.5	0.8	0.5	0.7	0.5
Pat glob 10	0.9	0.6	1.0*	0.5	1.0*	0.5
Pat glob 11	0.8	0.4	0.8	0.4	0.8†	0.4

Abbreviations: V, visit; V9, 24 weeks; V10, 28 weeks; V11, 32 weeks; Phy fct, physical function; Pat glob, patient global.

* $P < .05$.

† $P < .10$.

and UK regions, and in Germany. Differences from placebo were statistically significant at a number of times for the total population and for German study sites. It should be noted that even though each of these regions (US + UK and Germany) numerically favored PCH over placebo, some individual sites in the United States and United Kingdom indicated placebo was slightly better than PCH; the sample sizes of individual sites were generally small, and therefore the mean values of efficacy variables of individual sites may not be stable.

In the subset of patients with baseline WOMAC pain score greater than 220 mm, results indicated that the overall population numerically favored PCH compared with placebo (Table 4), similar to the findings in the patients with more severe disease in the categorical patient global assessment. When this subset of patients with baseline pain scores greater than 220 mm was broken down by region, the German sites generally favored PCH; the combined US and UK region sites, however, showed equivocal results. Statistically significant improvements for pain and physical function at 28 and 32 weeks were noted in the German sites; improvement in patient global assessment was not statistically significant.

For other subsets, patients aged 65 years or older; men versus women; and radiologic severity grade 2 versus grade 3, subset results did not differ from the initial total population analyses. Similarly, there were no statistical differences between PCH and placebo in any comparisons of results for 20%, 30%, and 40% responders.

Results of the completers and protocol nonviolators analyses were similar to those of the ITT population. Specifically, there was no statistically significant difference between treatments in the completer or protocol nonviolator analyses for the mean score between baseline and final treatment visit for pain, physical function, or patient global evaluation. Once again, however, results related to improvement in pain physical function and patient global evaluation showed statistically significant treatment effects in favor of PCH at the German sites. Secondary variables showed no differences amongst the various populations.

Safety Evaluation

Safety evaluation indicated a total of 278 patients (137 patients in the PCH group and 141 patients in the placebo group) who reported adverse events (AE). No severe AE was assessed as related to the study medication. Of the possibly or probably related AEs, most were mild to moderate gastrointestinal complaints (Table 5). There were no clinically significant increases or decreases in laboratory values, changes in vital signs, or physical examinations. Safety data from this study suggest that PCH is safe and well tolerated in patients with OA of the knee.

Table 4: Differences in Adjusted Mean Score for Pain, Physical Function, and Patient Global Responses Between Baseline and Visits 9, 10, and 11 (24, 28, 32 Weeks) for Patients With Baseline WOMAC Pain Scores 220 mm or Greater (ITT Analysis)

	PCH US + UK	Placebo US + UK	PCH Germany	Placebo Germany	PCH All	Placebo All
Pain—9	73.4	80.34	76.1	34.9	75.9	60.2
Pain—10	72.3	68.8	95.3*	33.4	84.2	53.4
Pain—11	68.1	64.9	91.8†	31.5	80.9	50.9
Phy fct 9	190.4	228.7	182.9	31.5	195.3	147.8
Phy fct 10	196.6	201.8	208.0†	17.0	211.8	126.9
Phy fct 11	172.2	175.0	209.3†	29.9	200.8	118.7
Pat glob 9	0.4	0.4	0.5	0.4	0.4	0.4
Pat glob 10	0.4	0.4	0.6	0.3	0.4	0.3
Pat glob 11	0.2	0.1	0.6	0.1	0.3	0.1

Abbreviations: V, visit; v9, 24 weeks; v10, 28 weeks; v11, 32 weeks; Phy fct, physical function; Pat glob, patient global.

* $P < .05$.

† $P < .10$.

Table 5: Number and Percentage of Patients With Adverse Events

	PCH				Placebo			
	Possible		Probable*		Possible†		Probable*	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Headache	1	0.5			1	0.5		
Diarrhea	3	1.5			5	2.6		
Nausea	2	1	1	0.51				
Peripheral edema	2	1			3	1.6		
Rash	2	1			1	0.5		
Flatulence	4	2	3	1.54	3	1.6		
Abdominal pain					1	0.5		
Sinus headache					1	0.5		
Arthritis aggravated								
Hypercholesterolemia	1	0.5						
Constipation	1	0.5			3	1.6		
SGOT increased	2	1						
Stools loose	2	1			1	0.5		
Creatinine kinase increased	1	0.5						
Dizziness					2	1		
Dyspepsia	1	0.5	1	0.51				
Heartburn					1	0.5		
Abdominal cramp	1	0.5						
Indigestion					1	0.5		
SGPT increased					2	1		
Gastritis	1	0.5						
LDH increased	1	0.5						
AP increase	1	0.5			1	0.5		
Pruritus	1	0.5			1	0.5		
Breast edema					1	0.5		
Neutropenia					1	0.52		

NOTE. Adverse events listed in order of decreasing frequency.

Abbreviations: SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; AP, alkaline phosphatase; LDH, lactate dehydrogenase.

* Probable relationship to study drug.

† Possible relationship to study drug.

Adverse Events

No study patient died during the course of the study. As noted, most AEs were mild to moderate in severity, with 23 events being reported as severe, 17 in the PCH group and six in the placebo group. No severe AEs were assessed as related to the study medication. Sixty-four AEs were considered possibly or probably related to the study medication, 32 in the PCH group and 29 in the placebo group. Of the possibly or probably related AEs, most were mild to moderate gastrointestinal complaints. Of the 389 subjects entered into the trial, 12 subjects discontinued the study medication because of an AE, three in the PCH group and nine in the placebo group.

DISCUSSION

The reasons for the differences observed in the efficacy of PCH in the United States and United Kingdom versus those in Germany are uncertain. Several explanations that might be considered include differences in diagnosis and recruitment between the sites, given that the United States/United Kingdom had rheumatologists as principal investigators, whereas orthopedists were the principal investigators in Germany. Nutritional differences

in the overall diet in these countries (eg, intake of gelatin-containing products over and above those administered during the study) also may have impacted the findings observed.

Although statistically significant differences between PCH and placebo were not noted when patients in all study sites were evaluated, statistical differences in efficacy were observed in patients with more severe symptomatology at the onset of the study with respect to both patient global assessment and assessment of baseline pain on the WOMAC pain scale. PCH was better than placebo in both the combined US and UK region, in addition to Germany, in the subset of patients whose baseline patient global evaluation rated as severe or extreme. In addition, in the subset of ITT patients with a WOMAC pain score greater than 220 mm, the overall population favored PCH compared with placebo. Similar findings related to efficacy in patients with more severe disease have been observed in other studies that evaluated symptomatic relief with therapeutic agents (32). Patients with more severe symptoms have greater potential for significant decreases in pain from baseline than patients with mild disease, in whom opportunity for a delta decrease in pain is more limited. Similarly, patients with milder disease are more likely to have a greater placebo response.

A role for PCH as a disease-modifying agent in the treatment of OA has been suggested, based on projected mechanisms of action relative to the role of collagen as a nutritional stimulant in other tissues (23-27). The current trial described previously in the United States, United Kingdom, and Germany did not assess changes in joint structure. However, the following recent study, designed to assess whether metabolism of proline as a component of collagen differed from metabolism of free proline with respect to cartilage localization, provides further information in support of a potential salutary effect of collagen on the cartilage matrix.

Animal Studies

Studies on the absorption of PCH were performed to address specific questions, including possible differences in the distribution of radioactivity in tissue subsequent to the absorption of ^{14}C-gelatin hydrolysate, and ^{14}C-proline (33). In studies performed by Oesser et al (33), test substances were administered by a gastric feeding tube. Mice of the gelatin group received 10 mg of ^{14}C-labeled gelatin hydrolysate/g body weight (580 Becquerel [Bq]/g body weight). In the control group ^{14}C-labeled proline (580 Bq/g body weight), was administered. Mice were killed from 3 to 192 hours after oral administration.

Qualitative investigations on absorption of hydrolysate were performed by using the "gut-sac" method for mice (C57/BL) and hamsters (34). Results showed a rapid increase of radioactivity in plasma, reaching a maximal concentration 6 hours after the beginning of the observation. More than 85% of plasma radioactivity disappeared after 24 hours (Fig 1A). Radioactivity in skin attained its peak value 12 hours after the administration of ^{14}C-labeled gelatin hydrolysate (Fig 1B) and, in contrast to plasma, radioactivity remained relatively high up to 96 hours. In plasma as well as in skin, radioactivity indicated no significant differences between the values obtained after administration of ^{14}C-labeled gelatin hydrolysate and the control group animals that had received ^{14}C-proline together with unlabeled gelatin hydrolysate. Studies in cartilage, however, showed significant differences between the gelatin and control groups (Fig 1C). Radioactivity in cartilage was significantly higher in mice that had received ^{14}C-labeled gelatin hydrolysate than in control animals.

In summary, in this study, gelatin hydrolysate was practically absorbed within 12 hours; a significantly higher degree of radioactivity was measured in cartilage subsequent to administration of ^{14}C-labeled gelatin hydrolysate than was the case with ^{14}C-labeled proline. Absorption of gelatin hydrolysate in its high-molecular-weight form was shown to have occurred. The accumulation of radioactivity in cartilage subsequent to administration of gelatin might represent a selective modification of cell metabolism. The authors suggest that the unique amino acid and peptide profile of gelatin may be responsible for clinical observations supporting therapeutic efficacy of orally administered gelatin in OA. As noted, the preferential uptake by cartilage suggests that PCH may play a positive role in cartilage metabolism.

Osteoporosis

Given the important role for collagen in bone structure, the effect of PCH on bone metabolism in persons with osteoporosis was evaluated (35). Investigation was designed to evaluate whether collagen hydrolysate added to calcitonin treatment led

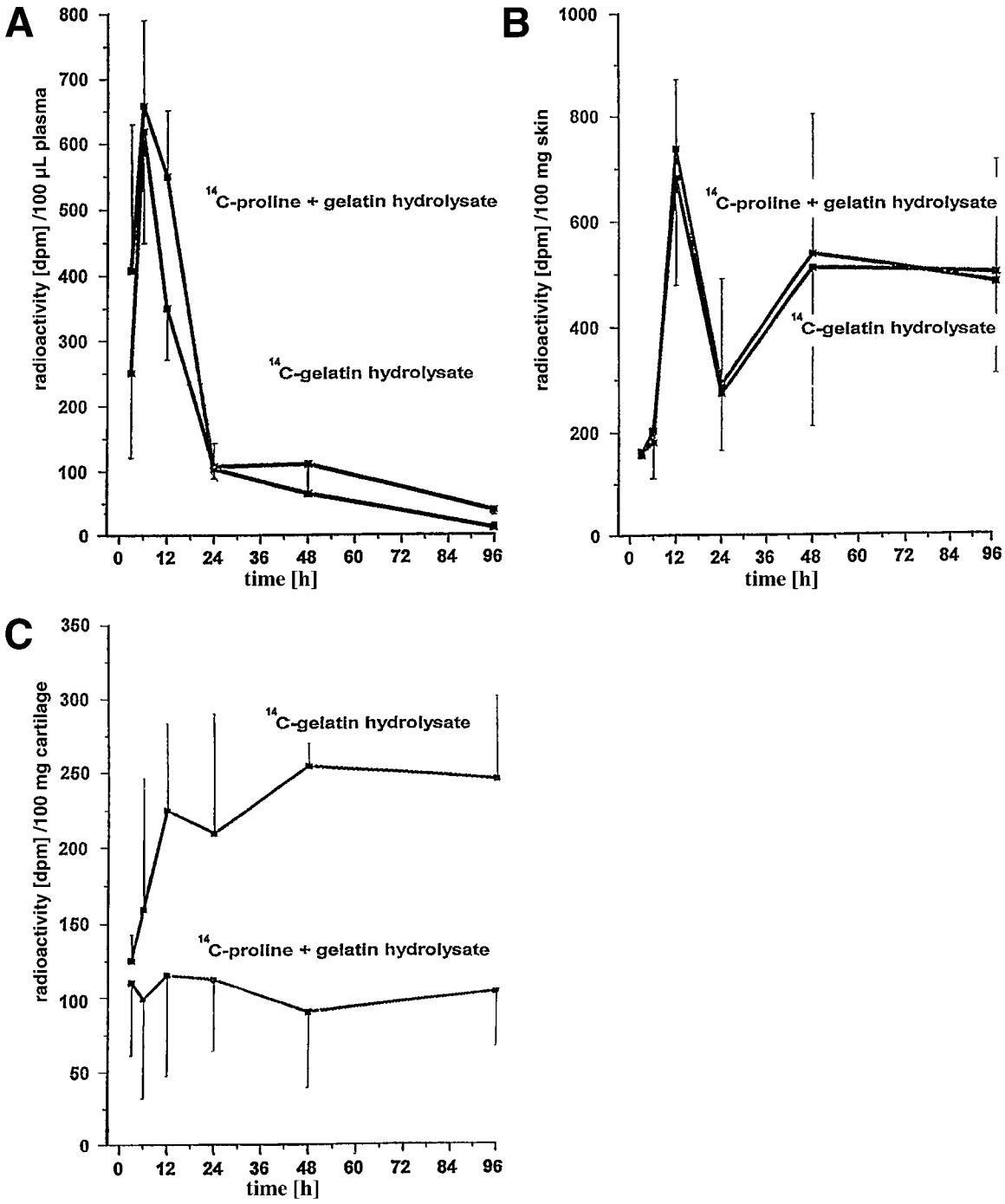

Fig 1. Radioactivity over time in (A) plasma, (B) skin, and (C) cartilage subsequent to absorption of ^{14}C-labeled gelatin hydrolysate and ^{14}C-labeled proline. The animals received a standard dose of radioactivity of 580 Bq/G body weight and 10 mg gelatin hydrolysate/G body weight. Mean values and SD for n = 6 are illustrated. (A) Radioactivity rapidly increases in plasma, reaching a maximal concentration at 6 hours. No significant differences were observed in results comparing ^{14}C-labeled gelatin hydrolysate and control animals that received ^{14}C-proline with unlabeled gelatin hydrolysate. (B) Radioactivity in skin attained its peak value at 12 hours and, in contrast to plasma, remained relatively high up to 96 hours. No significant differences were observed in results comparing ^{14}C-labeled gelatin hydrolysate and control animals that received ^{14}C-proline with unlabeled gelatin hydrolysate. (C) Radioactivity in cartilage was significantly higher in mice that had received ^{14}C-labeled gelatin hydrolysate than in control animals receiving ^{14}C-proline with unlabeled gelatin hydrolysate. (Reprinted with permission from the Journal of Nutrition, American Society for Nutritional Services [33]).

to greater improvement in bone collagen metabolism than calcitonin administration alone; urinary cross-link excretion was assessed to reflect the metabolic effects of these therapeutic approaches. Patients were evaluated clinically and with routine radiologic study, as well as by bone mineral density measurements using single-photon absorptiometry, and urinary pyridinoline and deoxypyridinoline excretion.

One hundred twenty-one postmenopausal women older than 40 years of age with radiologic evidence of osteoporosis, and bone mineral density less than 80% of normal, were recruited for participation in the study. Of these patients, 27 discontinued therapy because of reactions to calcitonin, including nausea, vomiting, and excessive flushing. Accordingly, 94 patients were evaluated, 47 in each group (calcitonin alone *v* calcitonin plus collagen hydrolysate). After a 6-month period of active therapy, 61 patients were further followed-up until 3 months after therapy ended, and densitometry and urinary pyridinoline and deoxypyridinoline studies were again performed. Patients were excluded from the evaluation in the presence of renal or hepatic dysfunction, or antiosteoporotic therapy in the year before onset of the trial. Patients with current corticosteroid therapy also were excluded.

All patients were treated with calcitonin (Calsynar, Rhone Poulenc C-Rorer), 100 units twice a week intramuscularly for 24 weeks. They were divided randomly into two subgroups, with 47 patients receiving a collagen hydrolysate-rich diet, and the second group receiving a lactose placebo, both in a dose of 10 g/d. Patients were demographically similar with respect to age, height, weight, number of pregnancies, onset and cessation of menses, and risk factors that include physical activity and use of alcohol, nicotine, or caffeine. Radiologic studies included radiographic evaluations of the right forearm and lumbosacral spine.

Bone density studies were performed on the distal right forearm by use of single-photon absorptiometry. Single-photon absorptiometry was performed with an osteometer DT 100 (Rodovre, Denmark). It employed a collimated beam of flow-energy photons from ^{125}Iodine, to assess bone mineral density. To ensure a homogenous layer of soft tissue around the bone to be measured, the forearm was placed in a water bath during the examination. Values of a Danish population were used as reference data. The evaluation of measured bone mass density were corrected according to age, sex, duration of postmenopausal period, weight, height, and dominant hand. Laboratory studies included serum calcium, phosphorus, alkaline phosphatase, and urinary calcium and phosphorus excretion.

Changes consistent with osteoporosis were present at study onset in all patients evaluated. In addition, codfish vertebrae were found in 33 individuals, and vertebral body fractures in 12. No statistically significant differences in radiologic assessment nor densitometry values were noted between the two groups after 6 months of therapy. Values of routine laboratory chemistry studies did

Table 6: Change in Pryidinoline and Deoxypyridinoline Urinary Excretion Over the 6-Month Study Period, Comparing Subjects Treated With Calcitonin Alone Versus Calcitonin Plus Collagen Hydrolysate

	Calcitonin Alone		Calcitonin + Collagen Hydrolysate	
Time (mo)	0	6	0	6
Number of patients	47		47	
	Mean (SD)		Mean (SD)	
Pyridinoline* (nmol/mmol creatinine)	104.1 (±37.9)	64.7 (±21.6)	115.0 (±65.4)	58.6 (±21.3)
Deoxypyridinoline* (nmol/mmol creatinine)	22.2 (±11.4)	16.7 (±27.9)	23.6 (±10.4)	11.6 (±4.9)

* Change in calcitonin alone *v* change in calcitonin + collagen hydrolysate, $P = .05$.

not change significantly during treatment. Urinary excretion of pyridinoline and deoxypyridinoline, measured as nmol/mmol creatinine, were elevated as compared with healthy adult controls at the onset of the study; values of both the pyridinoline and deoxypyridinoline markers decreased during the 6 months of therapy in both groups (Table 6). The two groups differed, however, in the amount of change in cross-link marker excretion from basal levels. Patients treated with a combination of calcitonin and PCH had a significantly greater fall in urinary cross-links as compared with patients treated with calcitonin alone ($P = .05$). Studies suggested accordingly that calcitonin plus PCH had a greater effect in inhibiting bone collagen breakdown than calcitonin alone. Decreased levels of urinary cross-links were maintained at the ninth month in both groups. These studies suggest that PCH had an additive effect relative to use of calcitonin alone in the treatment of patients with osteoporosis.

In summary, collagen hydrolysate is of interest as a therapeutic agent of potential utility in the treatment of OA and osteoporosis. A carefully controlled multinational study of symptomatic relief of OA using PCH in a dose of 10 g/d indicated that a subset of patients evaluated in several clinics in Germany showed a statistically significant improvement in pain relief. In addition, increased efficacy for PCH as compared with placebo was observed in the overall study population amongst patients with more severe symptomatology at study onset. Preferential uptake of radiolabeled proline in collagen hydrolysate, as compared to labeled free proline, suggests potential for a salutary effect on cartilage matrix. PCH may be of value in the treatment of osteoporosis based on clinical studies that showed an increased therapeutic response when PCH was added to calcitonin. The high level of safety of collagen hydrolysate makes it attractive as a potential therapeutic agent in both OA and osteoporosis; further trials will be looked on with interest.

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