Collagen-derived dipeptide, proline-hydroxyproline, stimulates cell proliferation and hyaluronic acid synthesis in cultured human dermal fibroblasts.

Ohara H, Ichikawa S, Matsumoto H, Akiyama M, Fujimoto N, Kobayashi T, Tajima S.

[Food and Health R&D Laboratories, Meiji Seika Kaisha, Saitama, Japan. hiroki_ohara@meiji.co.jp]

Abstract

Orally ingested collagen undergoes degradation to small di- or tripeptides, which are detected in circulating blood 2 h after ingestion. The influence of collagen-derived peptides on dermal extracellular matrix components and cell proliferation was studied using cultured human dermal fibroblasts. Of the various collagenous peptides tested here, the dipeptide proline-hydroxyproline (Pro-Hyp) enhanced cell proliferation (1.5-fold) and hyaluronic acid synthesis (3.8-fold) at a dose of 200 nmol/mL. This was concomitant with a 2.3-fold elevation of hyaluronan synthase 2 (HAS2) mRNA levels. Small interfering RNA (siRNA)-mediated knockdown of the HAS2 gene in human dermal fibroblasts inhibited Pro-Hyp-induced HAS2 mRNA transcription and cell mitotic activity. Addition of genistein or H7, a protein kinase inhibitor, abolished the Pro-Hyp-induced HAS2 mRNA stimulation. Pro-Hyp elevated phosphorylation of signal transducer and activator of transcription 3 (STAT3) within a short time period (60 min). These results suggest that Pro-Hyp stimulates both cell mitotic activity and hyaluronic acid synthesis, which is mediated by activation of HAS2 transcription.

Improvement in the Moisture Content of the Stratum Corneum Following 4 Weeks of Collagen Hydrolysate Ingestion

[Nippon Shokuhin Kagaku Kogaku Kaishi 56(3), 137-145, 2009-03-15
Japanese Society for Food Science and Technology]

Abstract

We conducted a placebo-controlled, double-blind 4-week study on the oral intake of either 3 doses of scaled collagen hydrolysate (2.5g, 5g and 10g), pig skin collagen hydrolysate (10g) or placebo in 214 healthy female volunteers (mean age, 34.1±SD 5.9 years). The volunteers were divided randomly into 5 groups and their skin condition was measured before and after ingestion. The moisture content of the stratum corneum of the cheek showed a significant increase after 4 weeks in all the groups taking the hydrolysates, while it showed a dose-dependent improvement in groups taking collagen hydrolysate (2.5g-10g). A stratified statistical analysis of subjects >30 years old showed significant differences in the groups taking 5g or 10g of hydrolysates ($P<0.05$), compared with the placebo group. There were no significant differences in transepidermal water loss, viscoelasticity or cutaneous findings between any of the groups. These results indicate that the major change following oral intake of collagen hydrolysate is an improvement in the moisture content of the stratum corneum.

Role of collagen hydrolysate in bone and joint disease.

Moskowitz RW

[Case Western Reserve University, Division of Rheumatic Diseases, University Hospitals of Cleveland, OH, USA.]

Abstract

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, doubleblind, 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 14C-labeled gelatin hydrolysate in cartilage as compared with administration of 14C-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.

Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucosamine, chondroitin sulfate, and collagen hydrolysate.

Deal CL, Moskowitz RW.

[Division of Rheumatology, Case Western Reserve University School of Medicine, University Hospitals, Cleveland, Ohio, USA.]

Abstract

There are a sufficient number of short-term studies with these agents suggesting efficacy equal to that seen in the symptomatic treatment of OA using NSAIDs. Two recent meta-analyses by McAlindon and colleagues and Towheed et al reviewed clinical trials of glucosamine and chondroitin in the treatment of osteoarthritis. The study by McAlindon and co-workers included all double-blind placebo-controlled trials of greater than 4 weeks' duration, testing oral or parenteral glucosamine or chondroitin for treatment of hip or knee osteoarthritis. Thirteen trials (six with glucosamine, seven with chondroitin) met eligibility criteria. The authors used global pain score or the Lequesne index in the index joint as the primary outcome measure and considered the trial positive if improvement in the treatment group was equal to or greater than 25% compared with the placebo group, and was significant (P < or = .05). All 13 studies reviewed were classified as positive, demonstrating large effects, compared with placebo (39.5% [S.D. 21.9] for glucosamine, 40.2% [S.D. 6.4] for chondroitin). The authors concluded that clinical trials of these two agents showed substantial benefit in the treatment of osteoarthritis but provided insufficient information about study design and conduct to allow definitive evaluation. Towheed and colleagues reviewed nine randomized, controlled trials of glucosamine sulfate in osteoarthritis. In seven of the randomized controlled trials, in which they compared glucosamine with placebo, glucosamine was always superior. In two randomized controlled trials comparing glucosamine to ibuprofen, glucosamine was superior in one and equivalent in one. Methodologic problems, including lack of standardized case definition of osteoarthritis and lack of standardized outcome assessment led the authors to conclude that further studies are needed to determine if route of administration is important and whether the therapeutic effect is site specific. A meta-analysis of chondroitin sulfate trials has also been published. Of the 12 published trials, 4 randomized double-blind placebo or NSAID-controlled trials with 227 patients on chondroitin sulfate were entered into the analysis. All four studies showed chondroitin sulfate to be superior to placebo, with respect to Lequesne index, visual analog scale for pain and medication consumption. Significant changes (P < or = .05) were seen in those treated from day 60 to the study endpoints (150 to 180 days). Pooled data demonstrated at least 50% improvement in the study variables in the chondroitin treated group. Discrepancies in some of the study findings reported in the literature may relate to the composition of the nutritional supplements used. Studies in the United States have revealed that a number of preparations claiming to contain certain doses of glucosamine or chondroitin sulfate have significantly less (or none) of the dosages described. Accordingly, it is essential that studies performed with these agents use preparations that are carefully defined in manufacture. The amounts generally administered are glucosamine, 1500 mg, and chondroitin sulfate, 1200 mg, daily. Although glucosamine has been described as effective when used alone, it is probably reasonable to use the combination pending further studies. The average cost is approximately $30 to $45 per month. In the interim, what should

physicians tell their patients when they ask whether these agents are effective, or whether they should or should not take them? The authors emphasize that these agents are not FDA-evaluated or recommended for the treatment of OA. They are available as health food supplements, and the number of studies of toxicity, particularly with respect to long-term evaluations, is limited. The pros and cons of these agents and the published data are described so that patients can make a reasonably informed decision as to whether they wish to proceed with use of these agents in therapy.

Ingestion of gelatin has differential effect on bone mineral density and body weight in protein undernutrition.

Koyama Y, Hirota A, Mori H, Takahara H, Kuwaba K, Kusubata M, Matsubara Y, Kasugai S, Itoh M, Irie S.

[Nippi Research Institute of Biomatrix, Nippi Inc., Tokyo, Japan. ykoyama@nippi-inc.co.jp]

Abstract

Malnutrition, particularly protein undernutrition, contributes to the occurrence of osteoporotic fracture by lowering bone mass. In this study, the effects of dietary protein on bone mineral density and body weight in protein undernutrition were compared between gelatin and milk casein. When mice were fed for 10 wk with a low protein diet containing 10(%) casein or 6% casein +4% gelatin, there was no significant difference in the final body weight between the 6% casein+4% gelatin group and the 10% casein group. In contrast, bone mineral content and bone mineral density of the femur were significantly higher in the 6% casein+4% gelatin group than in the 10% casein group. Bone mineral content and bone mineral density did not differ significantly in 14% protein groups between 14% casein and 6% casein +80% gelatin. These results suggest that gelatin has differential effects on bone mineral density and body weight in protein undernutrition.