ABSTRACT

Background: Collagen hydrolysate is a nutritional supplement that has been shown to exert an anabolic effect on cartilage tissue. Its administration appears beneficial in patients with osteoarthritis.

Objective: To investigate the effect of collagen hydrolysate on activity-related joint pain in athletes who are physically active and have no evidence of joint disease.

Design and setting: A prospective, randomized, placebo-controlled, double-blind study was conducted at Penn State University in University Park, Pennsylvania. Parameters including joint pain, mobility, and inflammation were evaluated with the use of a visual analogue scale during a 24-week study phase.

Study participants: Between September 2005 and June 2006, 147 subjects who competed on a varsity team or a club sport were recruited. Data from 97 of 147 subjects could be statistically evaluated.

Intervention: One hundred and forty-seven subjects (72 male, 75 female) were randomly assigned to two groups: a group \((n = 73)\) receiving 25 mL of a liquid formulation that contained 10 g of collagen hydrolysate (CH-Alpha)* and a group \((n = 74)\) receiving a placebo, which consisted of 25 mL of liquid that contained xanthan.

Main outcome measures: The primary efficacy parameter was the change in the visual analogue scales from baseline during the study phase in relation to the parameters referring to pain, mobility, and inflammation.

Results: When data from all subjects \((n = 97)\) were evaluated, six parameters showed statistically significant changes with the dietary supplement collagen hydrolysate (CH) compared with placebo: joint pain at rest, assessed by the physician \((-1.37 ± 1.78 \text{ vs. } -0.90 ± 1.74 \quad (p = 0.025))\) and five parameters assessed by study participants: joint pain when walking \((-1.11 ± 1.98 \text{ vs. } -0.46 ± 1.63,\)
Introduction

Collagen hydrolysate (CH-Alpha)* is a dietary supplement that may be beneficial in patients suffering from degenerative joint disease. Its use in the treatment of individuals with osteoarthritis (OA) has increasingly gained support in the medical community and among consumers. Collagen hydrolysate is made out of collagenous tissue from porcine sources such as bone, hide, and hide split. It is a product that is obtained when these raw materials are subjected to technical processes including extraction, enzymatic hydrolysis, purification, concentration, sterilization, and drying.

From the chemical point of view, collagen hydrolysate consists of proteins that range in size from 0.5 to 13.5 kilodaltons (kDa), with an average size of 3.3 kDa. It is a nongelling substance and can be easily dissolved in cold water.

In the past two decades, there has been an increased understanding of the effects of collagen hydrolysate on joint tissues in various models. Oesser et al., in a series of preclinical studies, demonstrated that collagen hydrolysate passes across the mucosal barrier in the small bowel as a complete peptide that is no longer subject to enzymatic cleavage, accumulates in cartilage tissue, and stimulates production of type II collagen (the major protein in articular cartilage) and proteoglycans in the extracellular matrix of cartilage11.3. In addition, they established a dose–response relationship between the concentration of collagen hydrolysate in which chondrocyte cultures are incubated and the quantity of type II collagen produced. This finding was confirmed by Ng et al., who used a three-dimensional approach to culture chondrocytes3.

In addition to these preclinical studies, open label, comparative, and prospective, randomized, placebo-controlled clinical trials and experimental findings have been published, with several studies providing evidence of a beneficial effect on measurements of joint health from the administration of collagen hydrolysate in a variety of patient populations5–12. Most of these clinical studies have been conducted in patients diagnosed with OA5–7,9–11. In the majority of these studies, investigators were able to demonstrate that the administration of 7–10 g of collagen hydrolysate per day for 3 months produced an improvement in measurements of joint health or function, such as reduction in pain,5,6,9 decreased dependency on pain medications,5 and improvement in leg strength11. Although these studies demonstrated reduction in joint pain in patients with OA treated with collagen hydrolysate, investigators wanted to determine the benefit of collagen hydrolysate in individuals with joint pain associated with athletic activities who had not been diagnosed with a medical disorder. To address this question, Flechsenhar et al. conducted an observational study of athletes with joint pain who did not have a diagnosis of OA at the Olympic training site (for German Olympic Games qualifiers) in Essen, Germany. Specifically, the aim of the study was to determine if treatment with 10 g/day of collagen hydrolysate would reduce joint pain in these athletes12.

One hundred athletes with exercise-related joint pain received 10 g/day of collagen hydrolysate for 12 weeks. Seventy-eight percent of the subjects in this observational study reported improved symptoms with reduction of pain on movement in 12 weeks. Similar percentages of patients reported improvements in pain while climbing stairs or pain when carrying objects. Parameters that were objectively assessed by the treating physician on a 1–10 pain scale (1 = no pain;
10 = severe pain) were also found to have similarly improved after 12 weeks.

The lack of a control group in this study limits the use of these data and prevents the conclusion being drawn that collagen hydrolysate is suitable as an agent for primary prevention purposes. However, the findings of this study suggested the importance of conducting another similar but well-controlled study. The aim of the current study is to extend these earlier findings with a more rigorous study design (that includes a control group) to determine if consuming a standardized preparation of collagen hydrolysate can reduce activity-related joint pain in athletes who do not have a diagnosis of OA.

Methods
Study design and population

This was a single-center, prospective, randomized, double-blind, placebo-controlled trial.

The original target was chosen to be 150 participants. Between September 2005 and June 2006, 147 individuals were recruited who were active as student athletes either on a varsity team or a club sport who complained about joint pain or joint discomfort due to joint stress, injury, surgical outcome, or trauma.

Potential subjects were excluded from the study if they met the following exclusion criteria:

- They did not have joint pain or joint discomfort
- They had an acute injury of a joint or an inflammatory process
- They ingested glucosamine, chondroitin, or other nutritional supplements that may be indicated for treatment of joint pain and OA
- People who from a clinical perspective were considered likely to increase their dose of analgesic medication during the 24-week study phase of the trial because of severe symptoms of arthralgia

The study was approved by the university IRB and students willing to participate signed informed consent.

According to the study schedule, after signing informed consent forms and randomization, the subjects were seen five times: for a baseline visit and four follow-up visits. Thus, the fifth visit corresponded with the subjects’ final evaluation. The study schedule contained a 6-week interval between two consecutive visits.

The randomization list was drawn up using the nQuery Advisor computer program version 5.0 (Statcon, Wittenhausen, Germany). Only one person, author K.F., had the codes for the randomization. The study participants were assigned to receive either 10g of collagen hydrolysate per day in the form of a vial containing 25 mL of a liquid formulation (n = 73) or a placebo that consisted of 25 mL of a liquid formulation containing xanthan (n = 74). The vials containing both the nutritional supplement and the placebo were indistinguishable from each other in terms of color, taste, or viscosity. A representative of the sponsor was the only person able to break the code.

During the baseline visit, a history was taken in relation to musculoskeletal diseases and subjects were given a physical exam. Questions were asked about the presence of pain in the knee, hip, shoulder, ankle, wrist, elbow, neck, and back. Apart from the location of the pain, data were collected concerning the cause of any joint pain, such as degenerative disease, sports injury, joint deformity, or genetic predisposition, and also the time span during which the subjects already had experienced pain in those respective joints (< 1 year, 1–5 years, 6–10 years or > 10 years).

A medical history was taken. Consumption of pain relievers, anti-inflammatory agents, cyclo-oxygenase II inhibitors, and other over-the-counter analgesics was recorded and information was collected in relation to alternative therapies like acupuncture, hydrotherapy, electric stimulation, massage therapy, joint conditioning/training, or topical application of ice or heat.

At the baseline visit, joint discomfort was recorded. Subjects’ complaints of joint discomfort were recorded using a visual analogue scale (VAS), which was divided into increments of 1 to 10 in relation to the severity of symptoms, with 1 = no manifestation of symptoms and 10 = very severe symptoms. The physician rated the following parameters: joint pain at rest, joint pain related to exertion, restricted ability to move, and state of inflammation.

Study participants rated their subjective symptoms using the same VAS scale. The degree of pain was self-rated, such as pain when walking, standing, running a straight line, running and changing direction, carrying objects, lifting, extending arms, rotating the shoulder, reaching and throwing, and at rest. The first five parameters were assessed when joints pertaining to the lower extremities were affected and the symptoms of the remaining parameters were recorded when joints of the upper extremities were affected.

When study participants presented for the following four visits, both the treating physician and the patients documented the objective and subjective findings as described for the initial visit. At each visit, patients were asked to provide information on consumption of pain relievers, anti-inflammatory agents, cyclo-oxygenase II inhibitors, and other over-the-counter analgesics. Information was collected on alternative therapies, including acupuncture, hydrotherapy, electric...
stimulation, massage therapy, joint conditioning/training, or topical application of ice or heat. The fourth follow-up visit (the fifth visit in the study) was considered the final visit and the end of the study. At baseline and each visit, subjects were given either the study treatment (collagen hydrolysate) or the placebo at baseline. They received either once-monthly or twice-monthly packages, depending on how many vials they had remaining from the previous visit. Compliance of medication was determined by asking participants to return all unused vials.

The primary end points of the study were defined as the comparison of the numerical differences of the scores of the VAS between both groups (collagen hydrolysate vs. placebo) after 24 weeks of treatment. These scores were calculated by subtracting the score of a particular parameter of visit 1 from the score recorded during visit 5. This method was applied to both the parameters assessed by the physicians and by the study participants.

**Descriptive analysis**

The parameters that were evaluated for both treatment groups were analyzed in a descriptive manner. The results were listed in tables, with nominal and categorical data indicated by absolute and relative frequency. Continuous data were listed as mean, standard error of the mean, median, standard deviation, variance, range, minimum and maximum.

**Confirmatory analysis**

A confirmatory analysis was carried out for the parameters that had been defined as primary end points. The scores that reflected the level of joint discomfort on the VAS were considered as continuous data. The test that was used to determine whether there was a difference between the two treatment groups was the non-parametric Mann–Whitney U-test. The significance level was defined to be $\alpha = 0.05$. A two-sided test was performed at all times to substantiate superiority of one group over the other. Because no hierarchy between the variables had been determined prior to the study, multiple testing was performed by adapting the significance levels according to the theory of Bonferroni–Holm.

For 15 separate tests, which were due to 15 separate primary end points, the global significance level of 0.05 had to be adapted to 15 local significance levels. According to Bonferroni–Holm, the calculated $p$-values appeared in rising order, the smallest $p$-value being listed first and the highest $p$-value being listed last. The smallest $p$-value was subsequently compared with the number 0.0033 (which is equivalent to $\alpha/15$), the second smallest $p$-value was compared with the number $\alpha/14$, and so on, up to the point where the highest $p$-value was compared with the number 0.05, which is $\alpha/1$. According to this theory, all the $p$-values that turn out to be smaller than the comparative number can be regarded as representing a statistically significant difference between the groups. The confirmatory analysis provided data in terms of statistical confirmed superiority or lack of statistical confirmed superiority for one of the treatment groups.

**Explorative analysis**

An explorative analysis was used to evaluate secondary end points. The $\chi^2$-test was chosen to determine whether there was a difference between both treatment groups. However, multiple testing was not performed for the secondary end points. The results of the explorative analysis are of a descriptive nature and do not provide any conclusion as to whether one treatment group is superior over the other group.

**Results**

In all, 147 individuals were recruited and gave informed consent to participate in the trial (Figure 1). Ten subjects were considered ineligible when they appeared for their first visit based on the treating physician’s or their own judgment because their joint discomfort had disappeared. Seventeen subjects did not present for the first visit and all the other visits and were lost to follow-up. Eight more participants were excluded from data management because of faulty documentation during the first visit. Four participants suffered an adverse event: two subjects suffered a new joint injury, one subject had to undergo surgery, and one subject was the victim of a car accident.

Eleven subjects presented fewer than three times for the scheduled visits, thus rendering a meaningful evaluation of their data impossible. In summary, 97 patients could be considered as the analysis population (46 (23 male, 23 female) receiving collagen hydrolysate and 51 (22 male, 29 female) receiving placebo). Twenty-five subjects out of these 97 participants presented fewer than five times for the scheduled visits, which consequently results in a per-protocol (PP) population of 72 individuals.

The baseline age, height, weight, and BMI of the study population showed no statistically significant differences between the treatment and placebo groups, as shown in Table 1. In addition, no difference between treatment group and placebo group could be observed in vitamin and mineral supplement use, although it approached significance ($p = 0.062$, data not shown).
The distribution of joint discomfort among various joints is shown in Table 2. The duration of pain was similar in both groups ($p = 0.565$, data not shown).

In 13 out of 97 subjects (13.4% of the analysis population), only one joint was affected by pain. The remainder of study participants had joint discomfort in two to eight joints. Each individual in the analysis population averaged arthralgia in 3.01 joints. For each joint that was affected by pain, the investigators used a separate sheet to collect data on the joint, so they were able to follow up on individual joints for each affected joint during the 24-week study phase.

The occurrence of pain in various joints was well-balanced between treatment groups (paired $t$-test for equivalence). The joint that most participants (63 subjects: 29 treatment, 34 placebo) indicated for joint discomfort was the knee.

After assessment at baseline, no significant difference between the treatment and placebo group was found for cause of pain, i.e., degenerative disease, sports injury, joint deformation, or genetic predisposition. No difference between groups was found ($p = 0.565$) for length of time for pain. Furthermore, when intake of medications (anti-inflammatory drugs, COX-II inhibitors, and other pain relievers) was analyzed, 15 out of 44 collagen hydrolysate patients, and 17 of the 49 placebo patients reported taking some form of medication. Therefore, no statistically significant difference between the treatment and placebo groups existed ($p = 0.951$).

The baseline severity of symptoms using a VAS ranging from 1 to 10 are shown in Table 3. Based on these results, the authors concluded that for the baseline visit, both groups were equal in severity of symptoms as assessed by the treating physicians, except for the parameter ‘restricted ability to move.’ As far as that particular parameter was concerned, the symptoms were judged as being less severe for the group receiving the nutritional supplement (collagen hydrolysate: $1.36 \pm 1.64$; placebo: $1.67 \pm 1.74$, $p = 0.038$).

In compliance with the study protocol, at baseline and at each visit participants rated the severity of various symptoms using a VAS that ranged from 1 to 10. The group of participants receiving the supplement was equal to the group receiving the placebo in terms of the severity of symptoms as judged by study participants (Table 4), except for the parameter joint pain when rotating shoulder ($p = 0.018$). This finding suggested that subjects receiving placebo had more severe symptoms than individuals receiving collagen hydrolysate in this one parameter at baseline.

### Primary efficacy outcomes

Interestingly, differences between groups became apparent at 24 weeks; those differences reached statistical significance for a number of parameters.

#### Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>All patients ($n = 97$)</th>
<th>Treatment</th>
<th>Placebo</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>20.1 ± 1.47</td>
<td>19.9 ± 1.50</td>
<td>20.3 ± 1.43</td>
<td>0.179</td>
</tr>
<tr>
<td>Male/female</td>
<td>45/52</td>
<td>23/23</td>
<td>22/29</td>
<td>0.499</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.80 ± 0.24</td>
<td>1.83 ± 0.32</td>
<td>1.77 ± 0.14</td>
<td>0.254</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.7 ± 17.8</td>
<td>77.9 ± 16.2</td>
<td>75.6 ± 19.2</td>
<td>0.530</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>23.9 ± 4.19</td>
<td>23.8 ± 4.36</td>
<td>23.9 ± 4.08</td>
<td>0.901</td>
</tr>
</tbody>
</table>
For the parameter joint pain at rest, which was based on the physicians’ judgment, collagen hydrolysate was statistically significantly superior to placebo (\(p = 0.025\) (CH: \(-1.37 \pm 1.78\), placebo: \(-0.90 \pm 1.74\))).

For the parameters walking (Figure 2), standing at rest (Figure 3), carrying objects, and lifting, which were all based on the study participants’ judgment, collagen hydrolysate was statistically significantly superior compared with placebo, with \(p\)-values of 0.007 (CH: \(-1.11 \pm 1.98\), placebo: \(-0.46 \pm 1.63\)), 0.011 (CH: \(-0.97 \pm 1.92\), placebo: \(-0.43 \pm 1.74\)), 0.039 (CH: \(-0.81 \pm 1.77\), placebo: \(-0.39 \pm 1.56\)), 0.014 (CH: \(-1.45 \pm 2.11\), placebo: \(-0.83 \pm 1.71\)) and 0.018 (CH: \(-1.79 \pm 2.11\), placebo: \(-1.26 \pm 2.09\)), respectively. As the study participants all improved (that is, they experienced decreased pain) during

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**Table 2.** Distribution of joint discomfort among various joints

<table>
<thead>
<tr>
<th>Joint</th>
<th>Collagen hydrolysate</th>
<th>Placebo</th>
<th>(p)-value (\chi^2)-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee pain: both knees</td>
<td>17</td>
<td>20</td>
<td>0.172</td>
</tr>
<tr>
<td>Knee pain: left knee</td>
<td>3</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Knee pain: right knee</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>No knee pain</td>
<td>15</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Hip pain: both hips</td>
<td>3</td>
<td>6</td>
<td>0.098</td>
</tr>
<tr>
<td>Hip pain: left hip</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hip pain: right hip</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No hip pain</td>
<td>33</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Shoulder pain: both shoulders</td>
<td>8</td>
<td>5</td>
<td>0.434</td>
</tr>
<tr>
<td>Shoulder pain: left shoulder</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Shoulder pain: right shoulder</td>
<td>10</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>No shoulder pain</td>
<td>23</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Ankle pain: both ankles</td>
<td>7</td>
<td>10</td>
<td>0.424</td>
</tr>
<tr>
<td>Ankle pain: left ankle</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ankle pain: right ankle</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>No ankle pain</td>
<td>25</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Wrist pain: both wrists</td>
<td>2</td>
<td>2</td>
<td>0.336</td>
</tr>
<tr>
<td>Wrist pain: left wrist</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Wrist pain: right wrist</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No wrist pain</td>
<td>26</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Elbow pain: both elbows</td>
<td>2</td>
<td>0</td>
<td>0.315</td>
</tr>
<tr>
<td>Elbow pain: left elbow</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Elbow pain: right elbow</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>No elbow pain</td>
<td>33</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Neck pain: no</td>
<td>28</td>
<td>28</td>
<td>0.797</td>
</tr>
<tr>
<td>Neck pain: yes</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Neck pain: not sure</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Neck pain: sometimes</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Back pain: no</td>
<td>21</td>
<td>20</td>
<td>0.639</td>
</tr>
<tr>
<td>Back pain: yes</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Back pain: I'm not sure</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Back pain: sometimes</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Collagen hydrolysate</td>
<td>21</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 3.** Severity of symptoms of patients (n = 97) at baseline, as rated by physicians

<table>
<thead>
<tr>
<th>Physician-rated symptoms</th>
<th>All subjects</th>
<th>Treatment subjects</th>
<th>Placebo subjects</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint pain at rest</td>
<td>2.12 ± 1.88</td>
<td>2.36 ± 2.14</td>
<td>1.87 ± 1.53</td>
<td>0.200</td>
</tr>
<tr>
<td>Joint pain related to exertion</td>
<td>5.36 ± 1.81</td>
<td>5.34 ± 1.88</td>
<td>5.39 ± 1.75</td>
<td>0.760</td>
</tr>
<tr>
<td>Restricted ability to move</td>
<td>1.52 ± 1.69</td>
<td>1.36 ± 1.64</td>
<td>1.67 ± 1.74</td>
<td>0.038*</td>
</tr>
<tr>
<td>State of inflammation</td>
<td>1.90 ± 1.52</td>
<td>2.03 ± 1.81</td>
<td>1.76 ± 1.16</td>
<td>0.675</td>
</tr>
</tbody>
</table>

*Indicates between-group difference < 0.05
the trial, regardless of whether they were part of the nutritional supplement or the placebo group, the absolute figures of the differences are always negative. So, the more negative a result, the more pronounced is the clinical improvement. These results imply that genuine differences in the evolution of pain scores were seen when the effect of collagen hydrolysate on joint discomfort was compared with placebo.

Next, we hypothesized that, by analyzing the scores of joint discomfort to one joint, the knee, we might find more clinically meaningful results. From the perspective of rheumatological research, a separate analysis of collagen hydrolysate’s effect on knee arthralgia appeared meaningful, as most clinical trials exploring the disease-modifying actions of investigational drugs focus on the knee.

Table 4. Severity of joint pain, as rated by patients at baseline. *Indicates between-group difference < 0.05

<table>
<thead>
<tr>
<th>Joint pain type</th>
<th>All subjects</th>
<th>Treatment</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>While walking</td>
<td>2.15 ± 1.97</td>
<td>2.37 ± 2.26</td>
<td>1.93 ± 1.61</td>
<td>0.562</td>
</tr>
<tr>
<td>When standing</td>
<td>2.04 ± 2.00</td>
<td>2.21 ± 2.16</td>
<td>1.87 ± 1.8</td>
<td>0.563</td>
</tr>
<tr>
<td>At rest</td>
<td>1.77 ± 1.80</td>
<td>1.92 ± 2.06</td>
<td>1.63 ± 1.48</td>
<td>0.893</td>
</tr>
<tr>
<td>When running a straight line</td>
<td>2.86 ± 2.13</td>
<td>2.93 ± 2.41</td>
<td>2.79 ± 1.82</td>
<td>0.769</td>
</tr>
<tr>
<td>When running and changing direction</td>
<td>3.43 ± 2.39</td>
<td>3.48 ± 2.58</td>
<td>3.38 ± 2.18</td>
<td>0.994</td>
</tr>
<tr>
<td>When carrying objects</td>
<td>2.88 ± 2.09</td>
<td>3.07 ± 2.32</td>
<td>2.69 ± 1.82</td>
<td>0.275</td>
</tr>
<tr>
<td>When lifting</td>
<td>3.69 ± 2.19</td>
<td>3.97 ± 2.38</td>
<td>3.42 ± 1.97</td>
<td>0.071</td>
</tr>
<tr>
<td>When extending arms</td>
<td>1.52 ± 1.85</td>
<td>1.51 ± 2.03</td>
<td>1.53 ± 1.66</td>
<td>0.094</td>
</tr>
<tr>
<td>When rotating the shoulder</td>
<td>1.54 ± 1.87</td>
<td>1.45 ± 1.99</td>
<td>1.64 ± 1.76</td>
<td>0.018*</td>
</tr>
<tr>
<td>When reaching</td>
<td>1.45 ± 1.64</td>
<td>1.44 ± 1.81</td>
<td>1.45 ± 1.47</td>
<td>0.141</td>
</tr>
<tr>
<td>When throwing</td>
<td>2.09 ± 2.23</td>
<td>2.03 ± 2.34</td>
<td>2.16 ± 2.13</td>
<td>0.164</td>
</tr>
</tbody>
</table>

*CH-Alpha

Figure 2. Change of pain perception for the parameter walking in the analysis population (n = 97) according to the visual analogue scale throughout the study phase (difference: score visit 5 – score visit 1) at 24 weeks. The numbers illustrated are the mean ± the 95% confidence interval. The larger the number, the greater the decrease in pain

*CH-Alpha

Figure 3. Change of pain perception for the parameter standing in the analysis population (n = 97) as recorded with the use of the visual analogue scale during the study (difference: score visit 5 – score visit 1) at 24 weeks. The numbers illustrated are the mean ± the 95% confidence interval. The larger the number, the greater the decrease in pain.
Data pertaining to 96 individuals were used for this post hoc subgroup analysis. In 18 subjects, there were data missing regarding all five scheduled visits. As an adverse event occurred in three individuals, those data had to be excluded from the analysis as well. In four study participants, data regarding the first visit were missing, so those subjects were also excluded from the statistical analysis, and eight individuals presented for less than three visits. Therefore, the final analysis subpopulation was equivalent to 63 subjects. Among those 63 individuals, 18 subjects presented either for three or four visits, which subsequently corresponds to a PP population of 45 study participants (Figure 4).

The 63 subjects whose data were used for a subgroup analysis had an average age of 20.1 years, an average height of 1.77 m, an average weight of 75.1 kg, and an average body mass index (BMI) of 23.8 kg/m². When the anthropometric data of the treatment group \( n = 29 \) and the placebo group \( n = 34 \) were compared by using a \( t \)-test, a difference in age could be noted between the groups \( (19.7 \pm 1.50 \text{ years vs. } 20.6 \pm 1.42 \text{ years} \ (p = 0.017)) \), which from the clinical point of view was irrelevant. Both groups were equal in relation to their use of medication \( (p = 0.768) \) and their use of alternative therapies \( (p = 0.458) \).

For the subgroup analysis, the parameters assessed by the physicians remained the same, as shown in Table 5, except for the parameter joint pain at rest \( (p = 0.028) \). This finding suggests that, except for the severity of this particular symptom, which was more severe for the participants in the collagen hydrolysate group, both groups were equal at the baseline visit in terms of the parameters that were assessed by the physicians.

From the perspective of the subjects, only five out of the 11 parameters recorded on the clinical report form were assessed for knee arthralgia, as those parameters focused on the severity of symptoms when the lower extremities were actively used.

\[
\text{Table 5. Patient parameters assessed by physicians, knee arthralgia subgroup analysis (} n = 63)\]

<table>
<thead>
<tr>
<th>Joint pain type</th>
<th>All subjects</th>
<th>Treatment</th>
<th>Placebo</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>2.28 ± 1.94</td>
<td>2.67 ± 2.23</td>
<td>1.91 ± 1.55</td>
<td>0.028</td>
</tr>
<tr>
<td>Related to exertion</td>
<td>5.41 ± 1.77</td>
<td>5.49 ± 1.82</td>
<td>5.34 ± 1.73</td>
<td>0.588</td>
</tr>
<tr>
<td>Restricted ability to move</td>
<td>1.44 ± 1.57</td>
<td>1.36 ± 1.56</td>
<td>1.52 ± 1.59</td>
<td>0.229</td>
</tr>
<tr>
<td>State of inflammation</td>
<td>1.98 ± 1.54</td>
<td>2.17 ± 1.80</td>
<td>1.80 ± 1.23</td>
<td>0.269</td>
</tr>
</tbody>
</table>

\[
\text{Table 6. Subjects’ self-report of symptoms of the lower extremities, subgroup analysis (} n = 63)\]

<table>
<thead>
<tr>
<th>Joint pain type</th>
<th>All subjects</th>
<th>Treatment</th>
<th>Placebo</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>When walking</td>
<td>2.32 ± 2.10</td>
<td>2.64 ± 2.45</td>
<td>2.02 ± 1.67</td>
<td>0.333</td>
</tr>
<tr>
<td>When standing</td>
<td>2.18 ± 2.07</td>
<td>2.43 ± 2.34</td>
<td>1.95 ± 1.77</td>
<td>0.565</td>
</tr>
<tr>
<td>At rest</td>
<td>1.96 ± 1.91</td>
<td>2.19 ± 2.22</td>
<td>1.74 ± 1.55</td>
<td>0.489</td>
</tr>
<tr>
<td>When running a straight line</td>
<td>3.00 ± 2.19</td>
<td>3.29 ± 2.60</td>
<td>2.74 ± 1.69</td>
<td>0.293</td>
</tr>
<tr>
<td>When running and changing direction</td>
<td>3.72 ± 2.42</td>
<td>4.02 ± 2.68</td>
<td>3.43 ± 2.11</td>
<td>0.096</td>
</tr>
</tbody>
</table>
Those parameters were joint pain when walking, joint pain when standing, joint pain at rest (subject’s perspective), joint pain when running a straight line, and joint pain when running and changing direction. These parameters are shown in Table 6. Apart from one parameter as judged by the physicians, the severity of symptoms was equivalent in both the group receiving the nutritional supplement and in the group being treated with the placebo.

When the primary end point was calculated on the basis of the analysis population for knee arthralgia, a statistically significant difference became apparent for the following parameters: joint pain at rest, with a $p = 0.001$ (CH: $-1.67 \pm 1.89$, placebo: $-0.86 \pm 1.77$) (Figure 5); joint pain when walking, with a $p = 0.003$ (CH: $-1.38 \pm 2.12$, placebo: $-0.54 \pm 1.65$) (Figure 6); joint pain when standing, with a $p = 0.015$ (CH: $-1.17 \pm 2.06$, placebo: $-0.50 \pm 1.68$); joint pain at rest (subject), with a $p = 0.021$ (CH: $-1.01 \pm 1.92$, placebo: $-0.47 \pm 1.63$); joint pain when running a straight line, with a $p = 0.027$ (CH: $-1.50 \pm 1.97$, placebo: $-0.80 \pm 1.66$); and joint pain when running and changing direction, with a $p = 0.026$ (CH: $-1.87 \pm 2.18$, placebo: $-1.20 \pm 2.10$).

### Secondary efficacy outcomes

When the intake of medication (anti-inflammatory drugs, COX-II inhibitors, and other pain relievers) was analyzed throughout the study for the analysis population ($n = 97$) at the final evaluation (visit 5), no difference between groups was seen ($p = 0.301$); however, when alternative therapies were analyzed, a statistically significant difference was noted between the collagen hydrolysate and the placebo group ($p < 0.001$). Specifically, at visit 5, the group taking collagen hydrolysate reported using alternative therapies 12 times, while subjects taking placebo reported using alternative therapies 39 times (Table 7).

The same results were found for the subgroup analysis ($n = 63$ subjects). No difference was noted in terms of the medication that was taken by the subjects at visit 5 ($p = 0.227$). However, a statistically significant difference was found between both groups when the use of alternative therapies was analyzed during the final visit ($p < 0.001$), with the collagen hydrolysate group reporting the use of alternative therapies 15 times compared with 30 times by the placebo group. This difference was only observed at visit 5 and not at the other four visits.

**Figure 5.** Change of pain perception for the parameter joint pain at rest (physicians’ judgment) for knee arthralgia in subgroup analysis population ($n = 63$) as recorded with the use of the visual analogue scale during the study (difference: score (visit 5) – score (visit 1)). The numbers illustrated are the mean ± the 95% confidence interval. The larger the number, the greater the decrease in pain.

**Figure 6.** Change of pain perception for the parameter joint pain when walking for knee arthralgia in subgroup analysis population ($n = 63$) as recorded with the use of the visual analogue scale during the study (difference: score (visit 5) – score (visit 1)). The numbers illustrated are the mean ± the 95% confidence interval. The larger the number, the greater the decrease in pain.
Adverse events
During the study, four adverse events were recorded. Two subjects (one CH and one placebo) suffered a new joint injury, one subject (placebo) had to undergo surgery and one subject (CH) had a car accident. None of the adverse events were determined to be treatment related. Since these adverse events interfered with an assessment of the study participants’ joint condition, the data pertaining to those subjects were excluded from statistical analysis.

Discussion

When taken orally by patients diagnosed with OA, collagen hydrolysate is a nutritional supplement that results in an increase of mobility, a decrease of pain, and a reduction in the dependency on analgesics. Studies of this supplement are available in the medical literature with more than 2000 patients who had experienced degenerative joint disease (reviewed in Bello and Oesser). However, many of these studies were open-label and/or did not provide statistical information in published reports. Also, the studies may be summarized as secondary prevention efforts, because they offer evidence suggesting the efficacy of the nutritional supplement in patients who had been diagnosed with OA.

The observational study that was performed by Flechsenhar and Alf with athletes from the Olympic Games site at Essen, Germany, was the first clinical study that investigated the use of collagen hydrolysate as a nutritional supplement to reduce symptoms of joint damage, with the hope that this change would reflect improvements in joint health. In that study, individuals were recruited who had not been diagnosed with degenerative joint disease but who complained about joint pain that both the treating physician and the subjects interpreted as being a result of stressful exercising. It was reported that 78% of individuals at the end of the study noticed substantial improvement of their joint symptoms. That finding could be numerically substantiated as the study participants at the Olympic Games site in Essen improved by up to five points on the visual analogue scale.

In spite of the fact that the results of the German observational study confirmed findings of previous well-controlled trials, the results of that study had the drawback that it did not include a control group. In rheumatology research, placebo effects and interpretations of efficacy of disease-modifying agents are closely intertwined and are sometimes hard to distinguish from one another. Consequently, the findings from the German observational study gave rise to the need for a placebo-controlled trial with athletes experiencing exercise-related joint pain. The result was the study described in this report.

The objective of this prospective clinical trial was to determine whether the administration of 10 g/day of collagen hydrolysate for 24 weeks, i.e. the same dosage and the same timespan that was defined in many OA trials, would translate into improvement of joint symptoms in individuals who did not have degenerative joint disease but who were physically active. Thus, recruiting young, healthy, and active individuals to participate in this research project was a crucial aspect of the trial.

From the 147 individuals who started the study, 97 subjects could be included in the analysis, which represents 66% of participants. From the perspective of a nutritional supplement study, a dropout rate of 34% is reasonable, underlining the willingness and the proactive attitude of the study participants to comply with the protocol.

Anthropometric data and information related to previous or present treatment modalities and the cause of pain revealed that the baseline characteristics of both the treatment and the placebo group were equivalent. The same was true when the subgroup of individuals complaining of arthralgia of the knee was submitted to an additional analysis.

When individuals with arthralgia of various joints were assessed during the baseline visit (visit 1) for the 15 parameters that were recorded on the visual analogue scales, apart from one parameter (pain when rotating shoulder), no difference of severity of symptoms was noted between the groups, which meant that a change in parameters during the 24-week study period would reflect an effect of the nutritional supplement collagen hydrolysate on joint symptoms.

The end point that yielded the most interest was the difference in scores for the analysis population (n = 97), when the findings of the final follow-up visit were compared with the status that was recorded during visit 1. Among the parameters that were evaluated, the parameter pain at rest as assessed by the physician (CH

<table>
<thead>
<tr>
<th>Patient group</th>
<th>n</th>
<th>Collagen hydrolysate</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis population</td>
<td>97</td>
<td>12</td>
<td>39</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Subgroup analysis population</td>
<td>63</td>
<td>15</td>
<td>30</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
vs. placebo (–1.37 ± 1.78 vs. –0.90 ± 1.74 (p = 0.025)) and the following five parameters as assessed by the study participants: joint pain when walking (–1.11 ± 1.98 vs. –0.46 ± 1.63 (p = 0.007)), joint pain when standing (–0.97 ± 1.92 vs. –0.43 ± 1.74 (p = 0.011)), joint pain at rest (–0.81 ± 1.77 vs. –0.39 ± 1.56 (p = 0.039)), joint pain when carrying objects (–1.45 ± 2.11 vs. –0.83 ± 1.71 (p = 0.014)) and joint pain when lifting (–1.79 ± 2.11 vs. –1.26 ± 2.09 (p = 0.018)) were found to be statistically significant. Thus, in each of these parameters, the subjects taking collagen hydrolysate reported less joint discomfort than subjects taking placebo.

When the use of alternative therapies was submitted to an analysis, it became apparent that there was a significant difference between the collagen hydrolysate and the placebo groups. As shown in Table 7, for the analysis population (n = 97), the collagen hydrolysate group reported using alternative therapies 12 times, while the placebo patients reported using alternative therapies 39 times (p < 0.001) during the final follow-up visit (visit 5). In the prior visits, no difference regarding alternative therapies was noted. These findings can be interpreted to indicate that it required more than 3 months for the effect of collagen hydrolysate to become clinically relevant from the point of view of a primary prevention approach. It appeared that the individuals who had been assigned to the placebo group were possibly lacking some beneficial effect that the subjects assigned to the nutritional supplement group perceived. The number of alternative therapies throughout the study decreased in the nutritional supplement group whereas it increased in the placebo group, thus graphically resembling two curves that diverted.

Because 65.3% of individuals initially recruited for the study (96 participants out of 147 who had signed the informed consent form), which corresponds to 64.9% on the analysis population (63 subjects out of 96), complained of arthralgia of the knee, and because most studies in rheumatology are exclusively standardized for the knee, a post hoc analysis for that particular joint was performed. The analysis of anthropometric data and the description of previous treatment modalities showed equivalence between the nutritional supplement and the placebo group and indicated that an analysis of that subgroup would reveal meaningful results. There was a difference in age between both groups (CH vs. placebo (19.7 vs. 20.6 years (p = 0.017)); however, from the clinical point of view, this difference would not be expected to produce any discrepancies in the study data.

When the primary end points for the analysis subpopulation (63 subjects) were considered, six out of nine parameters were statistically significant. Again, it was the parameter joint pain at rest that was assessed by the physician with a p = 0.001 (–1.67 ± 1.89 vs. –0.86 ± 1.77), plus the remaining five parameters that were based on the participants’ assessments, such as joint pain when walking with a p = 0.003 (–1.38 ± 2.12 vs. –0.54 ± 1.65), joint pain when standing, with a p = 0.015 (–1.17 ± 2.06 vs. –0.50 ± 1.68), joint pain at rest with a p = 0.021 (–1.01 ± 1.92 vs. –0.47 ± 1.63), joint pain when running a straight line, with a p = 0.027 (–1.50 ± 1.97 vs. –0.80 ± 1.66) and joint pain when changing direction with a p = 0.026 (–1.87 ± 2.18 vs. –1.20 ± 2.10).

The use of alternative therapies also appeared to be important when considered as a secondary outcome parameter. During the final follow-up visit (visit 5), participants assigned to the placebo group had a clear preference for using this therapeutic modality (30 times for the placebo patients compared with 15 times for the collagen hydrolysate patients, p < 0.001) (Table 7).

These results indicated that administration of 10g/day of collagen hydrolysate for 24 weeks translated into improvement of joint symptoms in individuals who did not have degenerative joint disease but who were physically active.

The findings of this study were analogous to the results that were shown in classical OA studies with collagen hydrolysate. In osteoarthritis, according to the results of previous studies, collagen hydrolysate starts to exert a beneficial effect on joint symptoms after a period of roughly 3 months. Approximately 80% of patients start perceiving an improvement of their joint symptoms after 10 or 12 weeks. In this study, a difference between the two groups did not become visible after 12 weeks; however, it became clearly apparent after 24 weeks. This also became evident when the secondary parameter alternative therapies was assessed. It was at the very end of the study that the placebo group increasingly used this modality. So, when the action of collagen hydrolysate on joint disorders is considered, a certain period of time must elapse before an effect manifests.

The parameter effect size (ES) is an important tool in research in rheumatology for assessing the magnitude of a therapeutic effect. It is defined according to the following formula:

\[
ES = \frac{\Delta_{\text{Active agent}} - \Delta_{\text{Placebo}}}{\text{Pooled standard deviation}}
\]

which means that the effect size represents a ratio that is calculated by determining the difference of the changes of a particular parameter exerted by the drug and the placebo, divided by the arithmetic mean of both standard deviations. If the effect size for a particular agent as determined by a parameter that may serve as the end point in a clinical trial is lower than 0.2, then the effect exerted by that agent
is considered weak. If it is higher than 0.8, it is considered strong.

When the effect size for the parameter joint pain when walking on the basis of the analysis population for all the joints \((n = 97)\) is calculated, the result corresponds to 0.36.

When the effect size for the same parameter is calculated on the basis of the analysis subpopulation for knee arthralgia \((n = 63)\), then the result is 0.45.

One should take into consideration that the subjects recruited for this study were healthy, young individuals. Consequently, the effect size that has been shown in this group of individuals may give a hint in regard to the potential that collagen hydrolysate has in view of a primary-prevention approach.

A limitation of the study was the lack of standardization in relation to sports activities. The investigators included several types of sports and did not randomize individuals by the activities they participated in. It may have been better to include only athletes involved in similar sports (e.g., football or basketball players); however, for practical reasons, this was not feasible.

**Conclusion**

The purpose of this study was to determine whether administration of 10 g/day of collagen hydrolysate would reduce joint pain in individuals with joint pain due to strenuous effort and physical exercise. For this research project, athletes of Penn State University were chosen as study participants.

The design of the study was appropriate to reveal that collagen hydrolysate as a nutritional supplement ingested over a period of 24 weeks by physically active young adults was efficacious in reducing symptoms of joint discomfort.

The results of this trial provide data supporting the view that collagen hydrolysate as a nutritional supplement may be administered to athletes to reduce the symptoms of joint pain associated with athletic activity. Taken together with preclinical studies which suggest that oral collagen hydrolysate reaches joints and stimulates joint tissues, athletes consuming collagen hydrolysate can potentially improve their joint health and reduce pain symptoms associated with strenuous athletic activity. Further research will clarify additional benefits from collagen hydrolysate.

**Acknowledgment**

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