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A randomized controlled trial on the efficacy and safety of a food ingredient, collagen hydrolysate, for improving joint comfort

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Abstract

Introduction Current options to promote joint comfort are limited to medicines that can reduce pain but can also have adverse effects. Collagen, a major component of joint cartilage, is found in the diet, particularly in meat. Its hydrolysed form, collagen hydrolysate (CH), is well absorbed. CH may stimulate the joint matrix cells to synthesize collagen, so helping to maintain the structure of the joint and potentially to aid joint comfort.

Methods In a randomized, double-blind, controlled multicentre trial, 250 subjects with primary osteoarthritis of the knee were given 10 g CH daily for 6 months.

Results There was a significant improvement in knee joint comfort as assessed by visual analogue scales to assess pain and the Womac pain subscale. Subjects with the greatest joint deterioration, and with least intake of meat protein in their habitual diets, benefited most.

Conclusion CH is safe and effective and warrants further consideration as a food ingredient.

Keywords: *Collagen hydrolysate, joint comfort, osteoarthritis, diet, meat*

Introduction

What is osteoarthritis?

Osteoarthritis (OA) is a disease of the cartilage, the tough elastic structure covering the extremities of bones. Cartilage alters progressively with age: small fragments detach, releasing foreign bodies within the joint that become sources of inflammation. The most frequently affected joints are those in the knees, hips, hands and vertebral column. OA is associated with joint discomfort, including pain, stiffness and swelling in the affected joints (Felson et al. 2000a).

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The prevalence of OA increases with age, affecting approximately 20% of individuals before the age of 45 years (Carmona et al. 2001). Radiographic signs of OA are estimated to be present in the majority of people by 65 years of age, affecting 80% of those over 75 years old (Arden and Nevitt 2006). OA is a major cause of work disability, especially for women over 50 years of age, and accounts for up to 25% of primary care visits (Arden and Nevitt 2006).

What is cartilage?

The surfaces where any two bones meet are covered with articular cartilage. This is a specialized, tough, flexible tissue with a smooth articulating surface of low friction resistance. These properties make cartilage ideally suited to load distribution, absorbing the shock of movement, avoiding friction and reducing wear and tear on bones. Articular cartilage is made of fibrous material with no blood or lymph vessels. It consists of chondrocytes (its only cells), which contribute about 2–10% to its volume, and an extracellular matrix, which is maintained by the chondrocytes.

The extracellular matrix consists of two components: tissue fluid and also a framework of structural macromolecules that enables the cartilage to fulfil its function of providing support and flexibility. The macromolecular framework consists of collagens (predominantly type II collagens), proteoglycans and non-collagenous proteins. The collagen fibres are arranged in the extracellular space near the surface of the cartilage. They are cross-linked by covalent bonds, forming a three-dimensional network, which provides tensile strength and resistance to shear.

Collagens contribute about 60% of the dry weight of cartilage, while the proteoglycans, which are embedded within it and give it elasticity and load-bearing properties, contribute about 25–35%. Non-collagenous proteins contribute about 15–20% (Creamer and Hochberg 1997; Eyre 2004; Eyre et al. 2006). The relative amounts of these cartilage constituents are crucial to the healthy function of the joint. Changes in their proportion and structural arrangement, arising from disease or injury, alter the mechanical properties of the cartilage and compromise joint comfort and function.

Rationale for collagen hydrolysate to promote joint comfort

Conventional drug treatments for OA, such as simple analgesics (e.g. acetaminophen) and non-steroidal anti-inflammatory drugs, attenuate symptoms but do not affect the underlying pathology of the disease. These drugs can also lead to adverse effects including gastrointestinal toxicity, increased risk of cardiovascular problems, renal and hepatic impairment and skin rashes. Surgical options for OA can minimize disability and more recent approaches to the treatment of OA have focused on the deceleration of cartilage deterioration (Felson et al. 2000b).

There is therefore a need for new active substances that could maintain joint comfort, function and mobility. Some substances such as glucosamine sulphate, chondroitin sulphate, diacerein are already used and have been shown to help to relieve joint discomfort and, in some cases, to modify structural changes (Najm et al. 2004; Clegg et al. 2006; Kim et al. 2006).

Collagen hydrolysate (CH) is a food ingredient that has the potential to improve joint comfort and function. Collagen itself is a natural component of the diet, found in animal products such as meat and fish. However, the absorption of orally ingested

collagen that has not been hydrolysed is poor. Collagen contains unique amino acids found in no other protein (namely hydroxyproline and hydroxylysine). The use of CH therefore provides amino acids specific to the collagen network, which could help to maintain the structure and function of joint cartilage, thus improving joint comfort in a safe and efficacious manner.

The fact that collagen is normally present in the diet, and that the food ingredient, CH, has been shown to be absorbed intestinally (Beuker and Rosenfeld 1996; Zeijdner 2002)—especially in fermented dairy products (Walrand et al. 2008)—and has been used for many years (as gelatine in foods) and declared safe (European Food Safety Authority 2005), makes CH an ideal ingredient for a functional food.

Previous evidence for efficacy of collagen hydrolysate

CH has been shown *in vitro* to significantly increase biosynthesis of type II collagen in chondrocytes in bovine (Oesser and Seifert 2003) and human (Oesser et al. 2006) cell cultures. Moreover, CH has been shown *in vitro* to significantly increase biosynthesis of proteoglycans in chondrocytes in humans (Oesser et al. 2006).

There have also been several reports that a daily intake of 10 g CH for 60 days or longer resulted in pain reduction in patients with OA of the hip or knee (Krug 1979; Oberschelp 1985; Seeligmuller and Heppel 1989; Adam 1991; Beuker et al. 1996; McCarthy et al. 2000; Moskowitz 2000; Zuckley et al. 2004; Carpenter et al. 2005a; Banzer et al. 2006; Bello and Oesser 2006). This effect is considered to be due to a specific effect of CH on joint tissues, since it is unlikely to have any analgesic or anti-inflammatory effects.

In a controlled intervention study of CH (Moskowitz 2000) conducted in the United States, United Kingdom and Germany, there was a discrepant result; benefits were seen in the German centres but not in the UK and USA ones (Selbmann et al. 2006). The question arose as to what extent dietary collagen, especially meat consumption, played a role in this finding.

We therefore conducted a randomized, double-blind, multicentre study comparing CH and placebo to evaluate the efficacy of CH in the management of joint discomfort in patients with OA of the knee, taking disease severity as well as diet into account.

Objectives

The primary objective was to evaluate the effect of the oral administration of CH on the osteoarthritis knee pain, considering a $\geq$30 mm reduction on the visual analogical scale (VAS) to be a significant answer.

The second objective was to evaluate the correlation between collagen tissue ingestion and the efficacy of the CH treatment.

Methods

Subjects: inclusion and exclusion criteria

A total of 250 patients were enrolled in six study centres in Ecuador. The sample size of 250 patients equally distributed between groups was calculated to detect a treatment difference of at least 30 mm on a VAS with a full range of 100 mm.

Male and female patients with primary OA according to the American College of Rheumatology criteria (Altman et al. 2000) and a score of between 30 and 50 on a 100 mm VAS for knee pain were considered for inclusion, which means patients with a light symptomatology. The reason was that CH is considered to collaborate in symptom alleviation but not to be a treatment as such. Moreover, the trial was designed to evaluate the effects of a functional food, not of a drug, so subjects with a low degree of OA were considered more representative of the targeted population.

Patients with Kellgren–Lawrence (KL) Grade I–III were included. Patients were excluded if they had a diagnosis of secondary OA, or if they had any concurrent or recent pharmaceutical or surgical treatment that would interfere with the interpretation of study results.

During screening, patients presented a recent knee X-ray; otherwise, one was performed at the centre to confirm the diagnosis of OA. Written informed consent was obtained, and patients were instructed on how to complete the questionnaires (see below).

Eligible patients were scheduled for three visits: baseline and treatment initiation (Visit 1), at 3 months (Visit 2), and 5 months after baseline (Visit 3).

A physical examination was performed at each visit, and patients were asked to report any concomitant medication. General laboratory tests were performed at Visits 1 and 3 to discard secondary OA or systemic diseases, and patients were asked about adverse events (AE) or morbidity events (ME) at Visits 2 and 3.

The study was approved by an independent Ethics Committee (Bioethics Committee, Central University of Ecuador, Protocol Number P-HC-E-2005) and all patients signed informed consent. The study was carried out in accordance with the Declaration of Helsinki, with local legislation and regulations governing clinical trials and with the requirements of Good Clinical Practice.

Questionnaires to assess knee pain and quality of life

Three questionnaires were used to measure health outcome in this study.

The VAS was used to assess pain intensity (Huskisson 1974). A score of 100 mm represented the most severe pain ever felt. The primary study endpoint was deemed to be the proportion of subjects who experienced a reduction in pain as defined by a decline of $\geq$30 mm on the VAS at 6 months. The large multi-centre Glucosamine/chondroitin Arthritis Intervention Trial (Clegg et al. 2006) used the criterion of reduction in pain (Pham et al. 2004) and showed significant decrease in pain in patients with moderate to severe OA with glucosamine and chondroitin sulphate in combination therapy compared with placebo, but not in the overall cohort. Similar findings emerged in a Spanish study where glucosamine was more effective than placebo in improving two types of pain score (Herrero-Beaumont et al. 2007).

The second questionnaire was the Western Ontario and McMaster Universities (WOMAC) Index, which is a self-report disease-specific measure with three dimensions—pain, disability and joint stiffness—for assessing osteoarthritis of the knee and hip. This was administered in the form of a five-point Likert scale. WOMAC is considered to be a valid, reliable and responsive measure of outcome and has been used in diverse clinical and interventional environments (McConnell et al. 2001). Moreover, WOMAC has been validated in several countries, including Spain (Escobar et al. 2002).

The third questionnaire was the 36-item Short-Form General Health Survey (SF-36). The SF-36 yields an eight-scale profile relating to physical pain, functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. The SF-36 instrument is considered to reflect the health-related quality of life (Ware and Sherbourne 1992) and has also been validated in Spain (Alonso et al. 1995).

Ingredients

The food ingredient used was Colnatur® (Protein SA, Girona, Spain), a powdered hydrolysed natural collagen with a mean molecular weight of 3,500 Da. It is sourced from traceable non-ruminant bones of neutral taste and odour, and is totally soluble in water.

Patients were randomly assigned to receive either 10 g CH or a matching amount of placebo (lactose) for once-daily administration dissolved in a liquid of the patient's choice. The 10 g dose was based on the scientific literature data of previous OA clinical studies (Krug 1979; Oberschelp 1985; Seeligmuller and Heppel 1989; Adam 1991; Beucker et al. 1996; Mc Carthy et al. 2000; Moskowitz 2000; Zuckley et al. 2004; Carpenter et al. 2005a; Banzer et al. 2006; Bello and Oesser 2006). CH and placebo were provided in pre-sealed, labelled envelopes to ensure randomization. Pain rescue medication consisted of 500 mg tablets of paracetamol, and the use of 3 g paracetamol for 10 or more consecutive days was considered treatment failure. Protocol violation was considered when the investigation project was not followed.

During the 3-month and 6-month visits, the patients were questioned about any AE or ME. The Scientific Committee analysed, *a posteriori*, whether these AE were related to the trial or not. To assess compliance, the patient was requested to return the empty envelopes of both the active product (CH) and the placebo as well as the acetaminophen tablets at Visits 2 and 3.

Food consumption

Meat intake was evaluated because the authors of a previous study suggested that the diet, particularly meat intake, may have contributed to their findings as meat is a significant source of dietary collagen (Moskowitz 2000). This randomized controlled trial, in which 389 patients with OA were given 10 g CH or placebo daily for 24 weeks, was conducted in the United States, the United Kingdom and Germany. A significant reduction in pain was reported only in the German centres (Moskowitz 2000). Although the authors thought that part of this discrepancy could be accounted for by the high dropout rate in the United Kingdom (42%) and the United States (37%) compared with Germany (7%), they also suggested that differences in diet may have been important. To address this possibility, a diary of food consumption was provided for completion in the 7 days prior to all three visits. A cut-off value of 1,549 g meat/week was chosen, corresponding to the median value.

These diaries were based on those used by the European Prospective Investigation of Cancer investigators (Bingham et al. 2001) and Harvard investigators (Willett et al. 1985).

Patients were asked to report all their meals and to estimate the quantity of each food ingested. By this means, food eaten at weekends as well as weekdays could be estimated and any seasonal dietary variations would be compensated for over the

6-month period. The average quantity of meat equivalent (in g/week) consumed in the three evaluations was calculated, and this value was used to divide subjects from the CH or placebo groups into two other subgroups based on the habitual amount of 'meat equivalent' consumed by all patients. This allowed an evaluation of the impact of CH in low and high meat eaters.

Statistical methods

An analysis describing the social–demographic and clinical characteristics of the patients subgroups included in the study was carried out in order to visualize the characteristics of the studied population.

The mean and standard deviation were used to describe the continuous variables; the patients' number and the patients' percentage by category of response were used to describe categorical variables. Data analysis was carried out using the statistical software SPSS v.14.0 for Windows.

In all of the statistical tests carried out with the results' variables, the significance level used was 0.05. Preliminary techniques were also used before running the tests previously described in order to assure the compliance of the statistical assumptions. When the fixed assumptions were not achieved, equivalent tests such as non-parametric ones were run.

To be able to evaluate the influence of the intake of animal-tissues' proteins on the dietetic habits of all the patients who finalized the study, the population was segmented into two subgroups, according to their equivalent meat intake: 'lower than' or 'higher+equal than' 1,549 g/week (median value of the variable equivalent meat intake in g/week).

At the end of the follow-up period, the VAS and WOMAC score changes were studied in each segment between the CH and placebo groups. At the end of the follow-up period, VAS and WOMAC score changes were analysed for each segment between the CH and placebo groups.

The Student's *t*-test and the Mann–Whitney U test were used to study the possible relation in each segment between the change of the different scales scores and the belonging or not to the CH or placebo subgroup, according to the characteristics of the studied variable and following the standard statistics.

Power calculation. On the basis of an α risk of 5% and a β risk of 20% in a bilateral contrast, 125 persons were required in each studied group to be able to detect a difference on the pain VAS higher than or equal to 30 mm. A maximum standard deviation was assumed. The follow-up losses rate was estimated at 30%. Therefore, 250 patients with knee arthritis had to be included, randomized in two groups of 125 patients each.

Statistical analysis of scores on questionnaires measuring pain. The difference between the scores on each of the instruments at the final and basal visits for the patients included in the analysis was described according to the mean and standard deviation of the mean. Comparisons of the VAS scores between the CH group and the placebo group and for each of the subgroups studied were made with the use of the non-parametric Mann–Whitney U test ($P=0.05$).

Similar comparisons on the WOMAC and SF-36 scores were made using the Student's *t*-test or the Mann-Whitney test ($P = 0.05$). Preliminary tests were applied prior to the statistical analysis to assure compliance with statistical principles. SPSS for Windows (version 14.0) was used for all statistical analysis.

Safety control

Safety of the product was followed up during the whole study (6 months) by the control of AE, morbidity (ME) and laboratory tests in Visits 1 and 3: complete blood count, coagulation, glucose, urea, urate, creatinine, transaminases, γ-glutamyl transferase, albumin, proteins, alkaline phosphatase and proteinurie. No significant differences were found between the CH and placebo groups.

Since CH is a food ingredient with a large history of use, declared safe by the European Food Safety Authority (2005) and considered Generally Recognized as Safe by the US Food Standard Agency, the safety study was not extended beyond 6 months.

Results

Compliance of subjects

As shown in Figure 1, 250 patients were randomized and distributed evenly between treatment groups. Of the 124 patients assigned to the placebo group, 96 (77%) completed the study—compared with 111 of 126 patients (88%) in the CH group.

Protocol violations were the most frequent cause of non-completion in the placebo group (13/28, 46.4%), whereas in the CH group the most frequent cause was loss to follow-up (6/15, 40%).

Baseline characteristics

Table I shows there were no significant differences in baseline characteristics between groups. All subjects who started the study and those with complete follow up are shown separately. The mean age was approximately 59 years, most were female. Radiological assessment showed KL Grade III in about 60% of patients.

Change in VAS for knee pain

Table II presents the results for change in VAS for knee pain of all subjects who completed Visit 3.

Intention-to-treat analysis was developed with the whole population, as it was proposed at the Investigation Memory, and no statistical significances were obtained.

The difference in the mean scores on the VAS for Visit 3 against baseline at Visit 1 on those who finished the study was 32.6 ± 14.3 mm in the CH group and 28.0 ± 16.8 mm in the placebo group. The difference between these two values was statistically significant ($P = 0.024$), indicating an improvement in joint comfort. Similar statistically significant ($P = 0.015$) differences were seen in the subgroup with most severe OA (KL Grade III). When habitual meat consumption was taken into account, patients with below-average meat consumption showed a significant ($P = 0.01$)

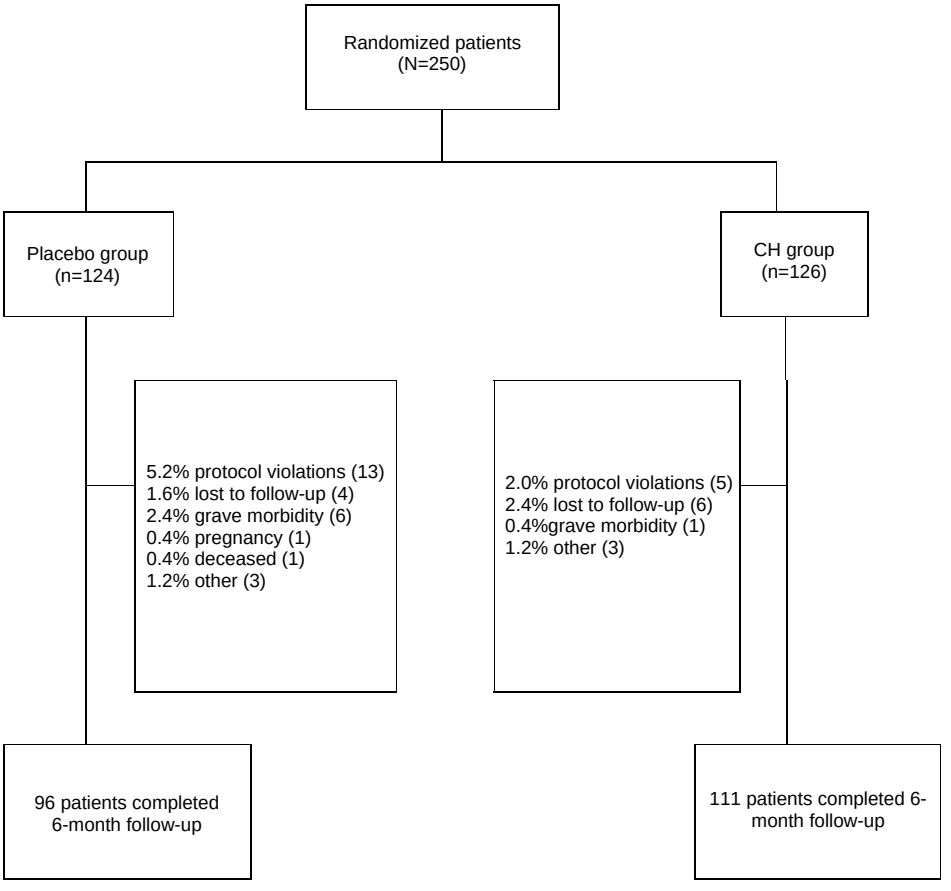

Figure 1. Patient distribution and compliance.

reduction in VAS, whereas there was no statistically significant treatment difference in VAS among patients consuming more meat than average.

Figure 2 shows the primary endpoint, deemed to be the proportion of subjects who experienced a reduction in pain as defined by a decline of ≥ 30 mm on the VAS. In the CH group 83 patients (75%) met this endpoint, compared with 51 patients (53%) in the placebo group; the difference between treatment groups was significant ($P = 0.001$).

Change in WOMAC and SF-36 scores

Table III shows that in the CH group there was a reduction in overall WOMAC score of 27.1 ± 18.1 (60%) points, compared with 18.9 ± 16.1 (56%) for placebo. The treatment difference was not statistically significant. Similar, non-statistically significant reductions between CH and placebo were found for WOMAC function and stiffness subscores.

However, the treatment group difference for the pain subscore was statistically significantly greater in favour of CH for all patients completing Visit 3. For WOMAC

Table I. Baseline demographic and disease characteristics.

	All randomized patients		Patients with follow-up	
	CH ($n=126$)	Placebo ($n=124$)	CH ($n=111$)	Placebo ($n=96$)
Age (years)	59.4±10.6	58.8±11.4	58.7±10.4	59.1±11.6
Females	117 (92.9)	114 (91.9)	103 (92.8)	89 (92.7)
Body mass index	27.2±4.3	28.2±4.4	27.1±4.1	28.3±4.6
Systolic blood pressure	124.0±12.7	125.3±14.3	124.0±11.8	125.2±14.5
Diastolic blood pressure	77.6±7.5	77.8±8.2	77.8±7.0	78.0±8.6
Years since diagnosis of OA	2.2±1.8	1.9±1.6	2.1±1.7	2.0±1.7
No prior surgical intervention	112 (88.9)	108 (87.1)	101 (91.0)	85 (88.5)
KL grade				
Grade I	18 (14.3)	17 (13.7)	14 (12.6)	13 (13.5)
Grade II	34 (27.0)	33 (26.6)	30 (27.0)	22 (22.9)
Grade III	74 (58.7)	74 (59.7)	67 (60.4)	61 (63.5)

Data presented as mean±standard deviation or *n* (%).

pain, the improvement between the first and final visits was 64% for CH and 53% for placebo. Compared with placebo, the improvement in WOMAC pain score between the two visits for CH was 19% ($P=0.044$). Statistically significant improvements in WOMAC pain score were also found among patients with OA rated radiologically as KL Grade III; improvement in WOMAC pain score between the two visits for CH over placebo was 41% ($P=0.021$)

When the patients were subdivided according to average meat consumption of more than 1.549 g/week animal protein, there was no statistically significant difference in WOMAC scores between CH and placebo for either low or high meat consumers.

Both the CH and placebo groups showed numerical improvement on all subscales of the SF-36 after 6 months, but with no statistically significant differences between treatment groups (data not shown).

Safety

A total of 50 ME was reported in the CH group and 31 in the placebo group. The most frequent ME was migraine headache, accounting for 9/50 (18.0%) events in the CH group and 5/31 (16.1%) for placebo. There were 29 gastrointestinal ME, 17/50 (34.0%) in the CH group and 12/31 (38.7%) in the placebo group. Five respiratory infections were reported in each treatment group. None of these ME was apparently related to the treatments.

Discussion

Joint comfort is important for good quality of life. The OA is the most common joint disorder worldwide. Radiographic evidence of OA occurs in the majority of people by 65 years of age and in about 80% of those aged over 75 years (Arden and Nevitt 2006).

Given that conventional drug treatments for joint conditions may need to be taken for prolonged periods of time and are also associated with adverse effects, the need for safer efficacious food ingredients is obvious. Moreover, joint damage is primarily due to

Table II. Change from baseline VAS for knee pain in patients with follow-up by subgroup.

	CH group				Placebo group				
	Visit 1	Visit 3	Absolute change	% change	Visit 1	Visit 3	Absolute change	% change	CH group versus placebo group *P* value
All patients with follow-up ($n=111$ CH and $n=96$ placebo)	43.1±7.4	10.5±13.1	−32.6±14.3	75.7	42.1±7.5	14.1±16.0	−28.0±16.8	66.5	0.024
KL grade III ($n=67$ CH and $n=61$ placebo)	40.5±7.0	10.8±13.5	−29.7±13.6	73.3	39.7±7.0	15.3±17.0	−24.4±16.0	61.5	0.015
Meat consumption <1,549 g/week ($n=59$ CH and $n=44$ placebo)	42.0±7.5	9.2±13.0	−32.8±14.4	78.1	42.2±7.4	17.8±18.8	−24.4±18.2	57.9	0.010
Meat consumption ≥1,549 g/week ($n=52$ CH and $n=52$ placebo)	44.4±7.2	12.0±13.1	−32.5±14.3	73.0	42.0±7.6	11.0±12.7	−31.0±15.0	73.7	0.486

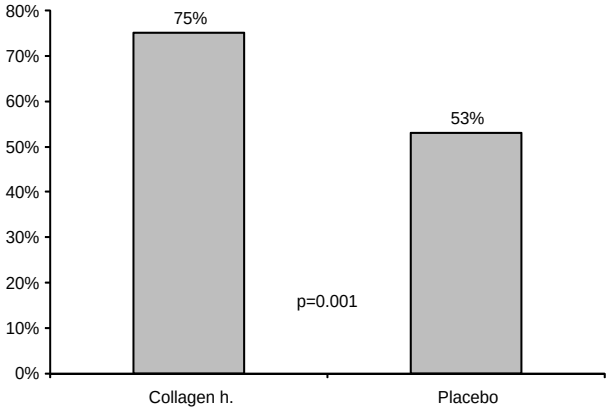

Figure 2. Proportion of patients in each group meeting the primary endpoint (at least 30 mm improvement on the VAS for knee pain).

changes in joint metabolism that lead to cartilage degeneration. Commonly used analgesic and anti-inflammatory drugs help to manage symptoms associated with joint damage but have limited effect on underlying joint pathology in conditions such as OA.

About 60% of the dry weight of cartilage is composed of collagen, and an ingredient that could help to maintain the structure of the collagen network could contribute significantly to the structure and function of the joint. CH is one such ingredient. It provides amino acids specific to the joint cartilage, is well absorbed when taken orally (Beuker and Rosenfeld 1996; Zeijdner 2002), accumulates in the cartilage (Oesser et al. 1999), and stimulates synthesis of the extracellular matrix by the chondrocytes (Oesser and Seifert 2003; Oesser et al. 2006). This is possibly the mechanism by which CH could help to maintain joint structure and function and help patients affected by joint disorders such as OA.

In the current study, analysis of the primary outcome measure, which was the proportion of subjects who experienced a reduction in pain as defined by a decline of $\geq$30 mm on the VAS, showed a significant difference ($P<0.001$) between the treatment (CH) and placebo groups (Figure 2). This clinically significant endpoint was reached by 75% of patients in the CH group but only 53% in the placebo group ($P<0.001$). Furthermore, a significantly greater pain improvement of patients in the CH group compared with placebo ($P=0.024$) was reported using the VAS.

The results of this study are also in agreement with those from previous controlled clinical trials in patients with various osteoarthritic conditions that have shown 10 g CH daily can improve subjective symptoms of arthritic conditions (Adam 1991; McCarthy et al. 2000; Zuckley et al. 2004; Carpenter et al. 2005a, Carpenter and Peel 2005b; Banzer et al. 2006).

The changes in WOMAC scores of all the patients that were followed-up are presented in Table III. On the pain subscale a change is observed in the CH group (63.8%) and a 53% change in the placebo group ($P=0.04$). The changes in placebo scores are comparable with those found in controlled trials evaluating drugs for osteoarthritis (Reginster et al. 2001; Pham et al. 2003; Herrero-Beaumont et al. 2007; Relchenbach et al. 2007). As it is suggested in the Gait trial (Clegg et al. 2006), the evaluation methods of the osteoarthritis activity index are poorly specific and change sensitive.

Table III. Change from baseline WOMAC score, patients with follow-up by subgroup

	CH group				Placebo group				
	Visit 1	Visit 3	Absolute change	% change	Visit 1	Visit 3	Absolute change	% change	CH group versus placebo group *P* value
All patients with follow-up ($n=111$ CH and $n=96$ placebo)									
WOMAC total	35.9±17.3	14.2± 12.6	−21.7±18.1	60.39	33.5±16.6	14.6±14.0	−18.9±16.1	56.44	0.252
WOMAC function	25.2±13.0	10.3±9.7	−15.0±13.7	59.30	23.2±12.7	9.9±10.0	−13.4±12.3	57.51	0.382
WOMAC pain	7.6±3.5	2.8±2.8	−4.9±3.9	63.80	7.2±3.4	3.3±3.3	−3.8±3.4	53.44	0.044
WOMAC stiffness	3.0±1.8	1.2±1.3	−1.8 ±2.2	60.90	3.1±1.5	1.3±1.6	−1.8±1.9	58.31	0.871
KL grade III ($n=67$ CH and $n=61$ placebo)									
WOMAC pain	6.8±3.0	2.3±2.1	−4.5±3.3	66.45	6.7±3.5	3.6±3.4	−3.2±3.2	47.03	0.021
Meat consumption <1,549 g/week		$n=59$				$n=44$			
WOMAC pain	7.0±2.9	2.7±2.7	−4.4±3.2	61.9	7.3±4.2	3.7±3.5	−3.6±3.1	49.2	0.240
Meat consumption ≥1,549 g/week		$n=52$				$n=52$			
WOMAC pain	8.3±4.1	2.9±2.9	−5.5±4.5	65.6	7.1±2.7	3.0±3.2	−4.0±3.6	57.2	0.079

In the current trial, treatment effects were also significant in the subgroup of patients with more severe joint disease. Among patients with radiological findings of KL Grade III, those in the CH group showed a significant improvement in pain compared with placebo on the VAS as well as the WOMAC pain scores ($P=0.015$ and $P=0.021$, respectively).

Patients with less than average meat consumption (<1,549 g/week) showed a significantly greater reduction of pain as measured on the VAS compared with placebo ($P=0.01$), but not on the pain subscale of the WOMAC scale; patients who consumed more meat (>1,549 g/week) did not show a treatment difference on either scale.

Patients with meat intake below the cut-off value had a significantly greater reduction in pain with CH than placebo, but patients with higher meat intake showed no such differences between CH and placebo. This indicates that CH could be of more benefit in people with low meat intake, and hence a relatively low intake of dietary collagen. Ingestion of CH could therefore be supplying the amino acids for collagen synthesis and stimulating the chondrocytes to produce the collagen matrix, particularly where intake of these amino acids is limited in a low-meat diet. The role of CH in patients with OA and low or high meat intake is worthy of further research.

Conclusion

Daily intake of 10 g CH for 6 months was safe and well tolerated. It results in a significant reduction in knee osteoarthritic pain as shown by VAS evaluation in all patients who completed the study ($P=0.024$). Analysis by the primary endpoint (a reduction of 30 mm or more in the VAS) was statistically significant ($P=0.001$). The treatment effects were also significant in patients with KL radiological grade III ($P=0.015$) and in the population with a daily meat intake of less than 1,549 g/week ($P=0.01$). Furthermore, the WOMAC subscale of pain showed a significant result in favour of patients who completed the study ($P=0.044$), and patients with KL grade III OA ($P=0.021$). Further studies with CH in patients with OA are warranted, and we suggest that daily meat intake should be considered an important parameter.

To sum up, the use of CH could help to protect the joints, reducing the risk of joint discomfort, so helping to maintain mobility and physical activity—it could cause a reduction of other types of management that can cause adverse effects. Thus the use of CH could reduce both social and healthcare costs to individuals and governments.

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