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Effect of collagen hydrolysate in articular pain: A 6-month randomized, double-blind, placebo controlled study☆

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KEYWORDS
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Summary
Objective: Evaluation of the efficacy and safety of a food supplement made of collagen hydrolysate 1200 mg/day versus placebo during 6 months, in subjects with joint pain at the lower or upper limbs or at the lumbar spine.
Design: Comparative double-blind randomized multicenter study in parallel groups.
Setting: 200 patients of both genders of at least 50 years old with joint pain assessed as ≥30 mm on a visual analogical scale (VAS).
Intervention: Collagen hydrolysate 1200 mg/day or placebo during 6 months.
Main outcome measure: Comparison of the percentage of clinical responder between the active collagen hydrolysate group and the placebo group after 6 months of study. A responder subject was defined as a subject experiencing a clinically significant improvement (i.e. by 20% or more) in the most painful joint using the VAS score. All analyses were performed using an intent-to-treat procedure.
Results: At 6 months, the proportion of clinical responders to the treatment, according to VAS scores, was significantly higher in the collagen hydrolysate (CH) group 51.6%, compared to the placebo group 36.5% ($p < 0.05$). However, there was no significant difference between groups at 3 months (44.1% vs. 39.6%, $p = 0.53$). No significant difference in terms of security and tolerability was observed between the two groups.
Conclusions: This study suggests that collagen hydrolysate 1200 mg/day could increase the number of clinical responders (i.e. improvement of at least 20% on the VAS) compared to placebo. More studies are needed to confirm the clinical interest of this food supplement.

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Introduction

Joint pain is a major cause of disability in subjects aged more than 50 years.[1] Symptomatic pain relief can be obtained with analgesics such as paracetamol, or non-steroidal anti-inflammatory drugs.[2] These treatments, while generally safe when used at low doses and for short terms, can result in serious complications (gastrointestinal bleeding, renal failure, coronary heart disease) when used for long-terms or at higher doses and could obviously reduce the adherence to therapy.[3,4]

In subjects with joint symptoms, food supplements are often taken by patients with the aim to relieve pain and improve physical functions.[5,6] However, it should be acknowledged that few well-designed studies support the clinical interest of these products. Moreover, most of these trials have been performed on patients with osteoarthritis.[7] However, food supplements, as over-the-counter products are used by the general population, without clear diagnosis of a disease. Consequently, well-designed studies to assess the efficacy of a food supplement to decrease the symptoms of the general population with joint problems would be useful.

GENACOL®, a food supplement made of collagen hydrolysate (CH), is a food supplement that claims to improve joint symptoms. The aim of the present study is to assess if the intake of this food supplement containing a proprietary CH during 24-week could increase the number of subjects with an improvement in joint pain and/or physical function symptoms.

Materials and methods

Study design and patients selection

In this 6-month double-blind randomized controlled trial, subjects received either CH (GENACOL®) in a daily dosage equivalent to 1200 mg of CH (i.e. 3 hard gel capsules per day) or a placebo (identical hard gel capsules, to be consumed in the same daily dosage). The randomization list was established with a computer assisted method by blocks of four.

Subjects were included if they were ambulatory Caucasian males or females aged 50 years or over, with joint pain (hip, knee, elbow, shoulder, hand or/and lumbar spine) over 30 mm on a 0—100 mm visual analogue scale (VAS). The target joint that was followed-up throughout the study was the most painful joint at the inclusion visit. As the product tested is a food supplement, no accurate diagnosis of joint pain was performed. General exclusion criteria included: any intra articular injection, whichever side, during the previous 3 months (6 months for hyaluronic acid) applied at the target joint; clinical evidence or suspicion, at the target joint, of septic arthritis, inflammatory joint disease, gout, Paget's disease of the bone or discal hernia; treatment with a chondroprotective agent (glucosamine sulfate, chondroitin sulfate) during the past 3 months.

The study was approved by the ethics committee of all participating study centres. All patients gave their written informed consent to participate. The study protocol was recorded on controlled-trials.com under the number ISRCTN76960238.

Outcomes assessment

Clinical assessments of the patients were performed at the baseline and after a follow-up of 3 and 6 months.

The primary objective of the study was to compare the percentage of responders between the active food supplement group and the placebo group. A responder subject was defined as a subject experiencing a clinically significant improvement (i.e. by 20% or more) in the most painful joint using the VAS score.

Secondary objectives were to compare between the two groups the consumption of pain rescue treatments, the pain/function changes, the health-related quality of life changes, the utility value changes and the tolerability and incidence of any adverse events.

Pain and function were assessed by the Lequesne index (hip and knee), the DASH score (upper arm) and the EIFEL questionnaire (Spine).

The Lequesne index evaluates pain or discomfort at the level of the knee or the hip, the maximum distance walked and activities of daily living.[8,9] Scores range from 0 to 24, with higher scores indicating greater disease severity. The Lequesne Index questionnaire is well recognized for its adequate validity, reliability, and responsiveness.

The DASH Outcome Measure is a 30-item, self-report questionnaire designed to measure physical function and symptoms in people with any of the several musculoskeletal disorders of the upper limb.[10]

The EIFEL questionnaire, also called the Roland—Morris questionnaire is a self-administered disability measure in which greater levels of disability are reflected by higher numbers on a 24-point scale.[11] The EIFEL questionnaire has been shown to yield reliable measurements, which are valid for inferring the level of disability, and to be sensitive to changes over time for groups of patients with low back pain.

Using these three questionnaires (i.e. Lequesne, DASH and EIFEL), another definition of clinical responder was defined. A responder subject was defined as a subject experiencing a clinically significant improvement in the most painful joint, according to one of the specific questionnaires: a reduction of at least 25% in Lequesne's index, a reduction of at least 5 points in the EIFEL's score[12] or a reduction of at least 12.7 points in the DASH's score.[13] The percentage of clinical responders in the active treatment group was then compared to that in the placebo group.

The EQ-5D health questionnaire is a generic instrument used to measure utility.[14] It contains a graduated visual analogue scale (VAS) from 0 (worst imaginable health state) to 100 (best imaginable health state).

General health status was measured with the Medical Outcomes Study 36-item short form Health Survey (SF-36).[15] The SF-36 consists of the measure of eight health dimensions (physical function, bodily pain, general health, vitality, mental health, social function, and role of physical and emotional health) in the conduct of daily activities. The SF-36 has been reported to have good validity, internal consistency, and reliability in the assessment of physical and mental health status of subjects and their progression.

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Table 1 Baseline characteristics.

	Collagen hydrolysate ($n = 100$)	Placebo ($n = 100$)	p-Value
Age (mean ± SD)	65.70 ± 7.83	64.44 ± 8.5	0.27
Gender (female/male %)	73/27	65/35	0.22
Clinical characteristics			
BMI (mean ± SD)	27.64 ± 4.67	27.60 ± 4.59	0.96
Target joint (%)			
Shoulder, elbow, hand	26%	22%	
Lumbar spine	27%	39%	
Hip	13%	11%	
Knee	34%	28%	

Statistical analysis

200 subjects were planned to be included in this study (100 in each group). This was based on the hypothesis of a difference of at least 40% between the two groups in the proportion of subject being considered as responder. A responder subject was defined as a subject experiencing a clinically significant improvement (i.e. by 20% or more) in the most painful joint using the VAS score. The pre-planned statistical power was fixed at 90%. We also hypothesized a drop-out rate of 15—20%.

Intent-to-treat (ITT) analyses were performed for all randomized patients, using the last observation carried forward approach. Dichotomous variables were reported using percentages. Descriptive statistics were reported as mean and SD for continuous normally distributed variables or as median and quartiles for non-normally distributed variables. Comparisons of categorical variables between collagen hydrolysate and placebo groups were performed with the use of the chi-square test. For continuous variables, the unpaired Student's t test and the Mann—Whitney test were used to compare differences between groups. All results were considered to be statistically significant if the corresponding p value was below 0.05.

Results

Baseline characteristics of the study population are reported in Table 1. No statistical significance was reported between the two groups.

The number of patients who withdrew for whatever reason from the study was well balanced between the two groups (Fig. 1). 56 patients withdrew (33 in the CH group, 23 in the placebo group): 15 were caused by adverse events (8 in the CH group, 7 in the placebo group), 24 were due to inefficacy (15 in the CH group, 9 in the placebo group), 13 were caused by nonmedical reasons (7 in the CH group, 6 in the placebo group), and 4 were lost to follow-up (3 in the CH group, 1 in the placebo group).

At 6 months, the proportion of clinical responders according to the VAS was significantly higher in the CH group (51.6%) than in the placebo group (36.5%) ($p = 0.036$) (Fig. 2). However, still according to the VAS, there was no significant difference in the number of clinical responders at 3 months (44.1% vs. 39.6%, $p = 0.53$). Likewise, with the definition of clinical responder based on specific questionnaire (i.e. Lequesne, DASH and EIFEL), no significant differences were observed between the two groups at 3 or 6 months.

We also looked at the proportion of clinical responders at 6 months according to the VAS by target joint (Table 2). Although it did not reach statistical significance, the median percentage change at 6 months in VAS scores was systematically higher in the treated group than in the placebo group, except for the knee. Moreover, at 6 months, a higher proportion of clinical responders, according to the VAS scores, were observed in the treated group for upper limbs ($p < 0.05$), lumbar spine ($p < 0.05$) and hip ($p > 0.05$), compared to the placebo group.

No statistically significant difference was observed between groups, neither concerning the utility value changes ($p = 0.54$), nor for any of the dimensions of the SF-36 questionnaire (p between 0.33 and 0.98).

Table 2 Proportion of clinical responders (%) at 6 months according to VAS by target joint.

	Collagen hydrolysate	Placebo	p-Value
Shoulder, elbow, hand	$n = 25$	$n = 22$	
% Clinical responders	60%	27.3%	0.024
Lumbar spine	$n = 24$	$n = 36$	
% Clinical responders	54.2%	27.8%	0.039
Hip	$n = 12$	$n = 11$	
% Clinical responders	66.7%	45.5%	0.305
Knee	$n = 32$	$n = 27$	
% Clinical responders	37.5%	51.9%	0.269

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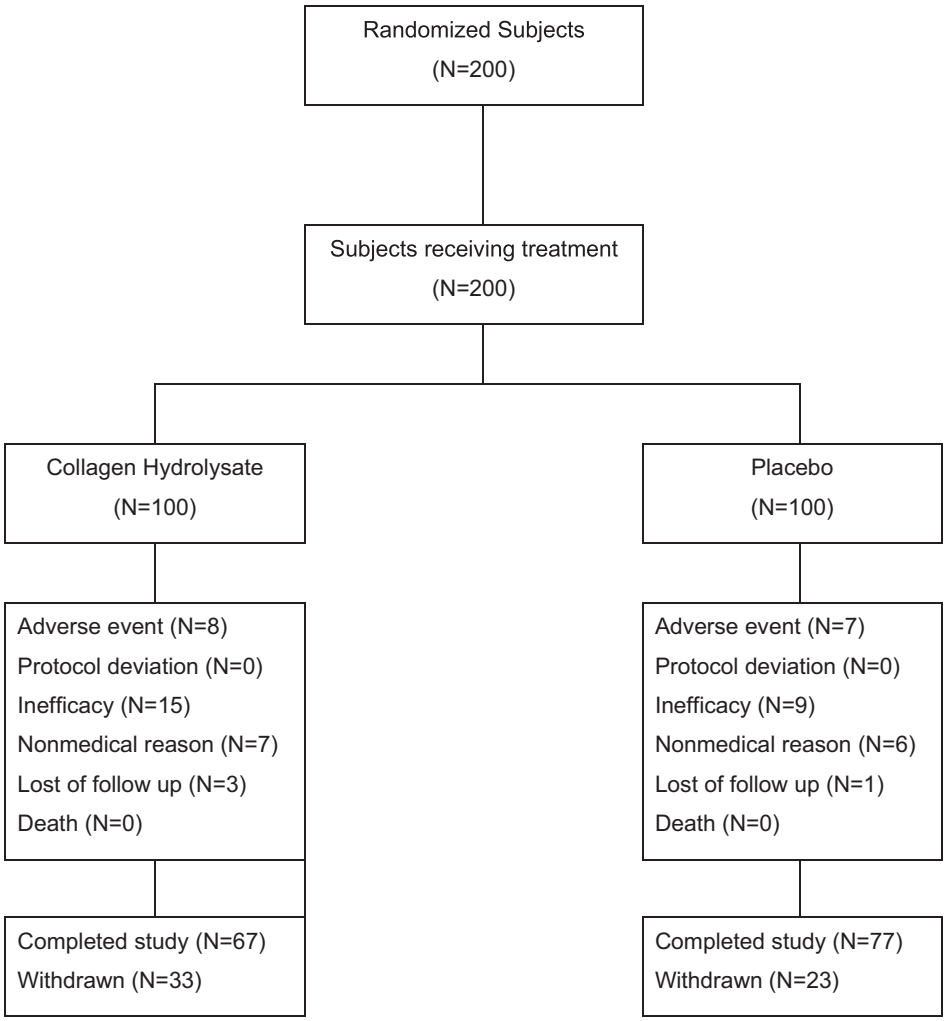

Figure 1 Disposition of subjects.

Most patients took a pain rescue treatment during their follow-up. In the CH and placebo groups, 69.4% and 78.3% respectively of the patients reported to take at least one pain rescue treatment during the study. There was no statistically significant difference in either the median number of pills taken or in the median duration of treatment, between groups.

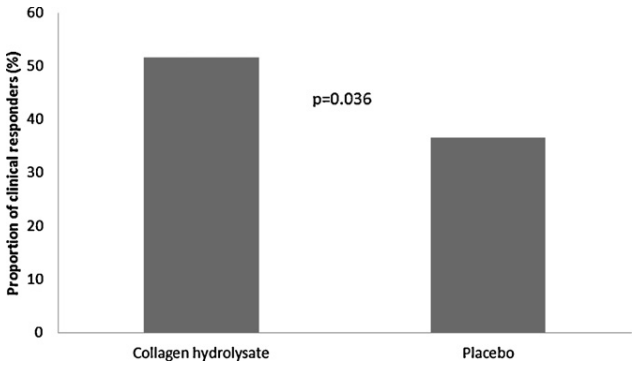

Figure 2 Proportion of clinical responders at 6 months according to VAS.

At 6 months, the satisfaction level in terms of efficacy was not statistically different in the two groups (Table 3). At each visit, a higher proportion of patients were moderately satisfied with their treatment. There was no statistically significant difference in terms of satisfaction about tolerability between groups, although there was some evidence that, in the majority of the patients, tolerability was judged in both groups as satisfactory or very satisfactory (Table 3).

There were no significant differences between groups in the number of subjects reporting at least one adverse event, in the incidence of serious adverse events, or in the incidence of adverse events considered to be possibly related to the study drug (Table 4).

Discussion

In this 6-month randomized placebo controlled study, we have been able to show that CH was able to increase the proportion of clinical responders, as defined by an improvement of at least 20% in the VAS score, compared to patients

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Table 3 Proportion of patients (%) according to their level of satisfaction in terms of efficacy and tolerability.

	Collagen hydrolysate	Placebo	*p*-Value
Satisfaction in terms of efficacy			
Very satisfied	12.5%	6.1%	
Satisfied	20.8%	25.5%	
Moderately satisfied	31.3%	30.6%	0.433
Dissatisfied	27.1%	24.5%	
Very dissatisfied	8.3%	13.3%	
Satisfaction in terms of tolerability			
Very satisfied	43.3%	40.4%	
Satisfied	35.1%	32.3%	
Moderately satisfied	13.4%	15.2%	0.258
Dissatisfied	8.3%	7.1%	
Very dissatisfied	0%	5.1%	

receiving placebo. However, using joint specific health related quality of life questionnaire, we have not been able to show a difference in the proportion of responders between the two groups. GENACOL, compared to placebo, was well tolerated with no significant differences between the numbers of adverse events.

There are strengths and limitations to this study. Strengths include the large number of subjects included in the study and the design of the trial. Limitations include the absence of a validated tool to assess joint pain in a healthy population and the drop-out rate, slightly higher than expected.

It should be pointed out that no significant beneficial effect of CH has been observed after 3-month and that this food supplement should be given for at least a 6-month period. In the available literature of CH, even if positive results with CH have already been observed after 14 weeks of supplementation the majority of the published trials have observed a significantly beneficial effect of CH over a 6-month period.[7] For example, a study recruited 147 individuals 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.[16] These subjects were randomized to receive either 10 g of CH 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 ($n = 74$). After 24 weeks of treatment, among the 15 primary outcomes, a statistically significant effect of CH compared to placebo was observed for joint pain at rest, walking, standing, at rest, carrying objects, and lifting. However, caution in interpreting these results is needed because no intention-to-treat analysis has been performed and because there were no significant differences between groups for any endpoint when significance levels were adjusted for multiple comparisons.

It is also important to note that the majority of the trials previously performed with CH have been performed in patients with osteoarthritis symptoms at the level of the knee.[7] For example, a large well-designed study randomized 389 patients with osteoarthritis to CH or placebo for a 24 weeks period.[17] Primary efficacy measures were the WOMAC pain dimension score, WOMAC physical function dimension score; and patient's global evaluation. There were no

Table 4 Proportion (%) of patients with at least one AE during the study, according to the AE class.

	Collagen hydrolysate	Placebo	*p*-Value
Sense (eyes, ears, taste, olfaction)	4.1%	3.0%	0.680
Cardio-vascular	3.1%	8.1%	0.129
Respiratory	15.5%	22.2%	0.227
Gastro-intestinal	15.5%	26.3%	0.063
Hepatic/biliary	0%	0%	
Genito-urinary/reproduction	5.2%	1.0%	0.092
Kidney/renal	0%	0%	
Endocrine/metabolism	2.1%	3.0%	0.667
Musculo-skeletal	23.7%	16.2%	0.186
Hematology/lymphatic	0%	0%	
Neurological/psychiatric	7.2%	8.1%	0.820
Dermatological	6.2%	4.0%	0.495
Immunological	1.0%	0%	0.311
Allergy	0%	0%	
Others	7.2%	6.1%	0.745

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statistically significant difference between treatments in the intent-to-treat analysis for the change of the mean score for pain between baseline and visit 9 (24 weeks) and for the evaluation of pain, physical function, or patient global assessment.

In our study, we have included subjects with joint pain, whatever the localization and the diagnosis. Indeed, as an over-the-counter product, no diagnosis of any disease has to be performed. Consequently, we have tried, in this study, to include subjects that are the targeted subjects of the product. Obviously, a substantial proportion of our study population has probably osteoarthritis, as in the general population.[18]

We acknowledge that for all our secondary outcomes, no significant differences were observed between CH and placebo. The discrepancy between the results observed using the VAS score and the specific questionnaires (i.e. Lequesne, DASH and EIFEL) could partly be explained by the specificity of these questionnaires (e.g. the Lequesne questionnaire was primarily developed as a predictive tool to evaluate the necessity of joint replacements). However, recent preclinical studies questioned the clinical interest of CH. For example, it was shown that 1 mg/ml CH may actually inhibit macromolecule biosynthesis and be detrimental to the mechanical properties of long term chondrocyte-agarose constructs.[19] Another study suggests that CH, as a media supplement, is not a viable long-term method to improve the collagen content of engineered cartilage tissue.[20] However, other in vitro studies have provided preclinical basis for in vivo testing of the efficacy of CH.[21] For example, it has been shown that CH is able to stimulate collagen synthesis in chondrocytes.[22]

We conclude that in this 6-month randomized placebo controlled study, CH is able to increase the proportion of clinical responders, as defined by an improvement of at least 20% in the VAS score, compared to patients receiving placebo. More well-designed clinical trials are needed to define the exact clinical interest of CH in subjects with joint pain.

Conflict of interest

O Bruyère receives grants or has been reimbursed for attending meetings from GlaxoSmithKline, IBSA, MSD, Novartis, Rottapharm, Servier, Theramex and Wyeth. He also gives advice to the European Food Safety Authority and the French Food Safety Agency. J-Y Reginster has received consulting fees or payments for participating in advisory boards for Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex, and UCB. He has received lecture fees when speaking at the invitation of Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, and Novo Nordisk; and grant support from Bristol Myers Squibb, Merck Sharp & Dohme, Rottapharm, Teva, Lilly, Novartis, Roche, GlaxoSmithKline, Amgen, and Servier. Other authors have no conflict of interest.

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