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European Journal of Physical and Rehabilitation Medicine 2016 June;52(3):321-30

ORIGINAL ARTICLE

The efficacy and safety of a combination of glucosamine hydrochloride, chondroitin sulfate and bio-curcumin with exercise in the treatment of knee osteoarthritis: a randomized, double-blind, placebo-controlled study

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ABSTRACT

BACKGROUND: Knee osteoarthritis (OA) conservative treatment aims to delay cartilage degeneration; chondroprotective agents are a valid approach in this sense. A commercially available dietary supplement, CartiJoint Forte, containing glucosamine hydrochloride (GH), chondroitin sulfate (CS) and Bio-Curcumin BCM-95®, was used in this trial.

AIM: The aim of this study was to assess efficacy and safety of CartiJoint Forte combined with physical therapy in treating subjects with knee OA.

DESIGN: A multicenter, prospective, randomized, double blind, placebo-controlled clinical trial.

SETTING: Outpatients referred to the Rehabilitation Departments of two University Hospitals.

POPULATION: Fifty-three patients were randomly assigned to an experimental group (N=26) or a control group (N.=27). Experimental subjects received two tablets of CartiJoint Forte each day for 8 weeks, while those in the control group were provided with a placebo. Three subjects dropped out during the course of the study.

METHODS: The two groups both received 20 sessions of physical therapy during the course of the trial. Primary outcome was pain intensity, measured both at motion and at rest, using the Visual Analogue Scale (VAS). A secondary outcome was an assessment of knee function by Western Ontario and McMaster Universities Arthritis Index and Lequesne Index, knee ROM, and two inflammation markers (C-reactive protein and erythrocyte sedimentation rate). Each assessment was carried out at baseline (T0), at 8 weeks (T1) and at 12 weeks (T2).

RESULTS: VAS at rest was found to be reduced between T0 and T1, as well as between T0 and T2 (F=13.712; P=0.0001), with no differences between groups (F=1.724; P=0.191). VAS at motion revealed a significant "group × time-check" interaction (F=2.491; P=0.032), with increasing effect of time on VAS reduction (F=17.748; P=0.0001). This was most pronounced in the experimental group at 8 weeks (F=3.437; P=0.045). The Lequesne Index showed reductions at T1 and T2 compared to T0 (F=9.535; P=0.0001), along with group effect, since the experimental group presented a lower score at T2 (F=7.091; P=0.009). No significant changes were found in the knee ROM and inflammation markers.

CONCLUSION: CartiJoint Forte, added to physical therapy, may ameliorate pain and help to improve algofunctional score in knee OA patients.

CLINICAL REHABILITATION IMPACT: Treatment of knee OA with curcuminoids plus glycosaminoglycans, added to physical therapy, improves VAS at motion and Lequesne Index scores.

(*Cite this article as:* Sterzi S, Giordani L, Morrone M, Lena E, Magrone G, Scarpini C, *et al.* The efficacy and safety of a combination of glucosamine hydrochloride, chondroitin sulfate and bio-curcumin with exercise in the treatment of knee osteoarthritis: a randomized, double-blind, placebo-controlled study. Eur J Phys Rehabil Med 2016;52:321-30)

Key words: Dietary supplements - Knee osteoarthritis - Physical therapy modalities - Pain management.

Osteoarthritis (OA) is a medical condition characterized by loss of joint cartilage; this leads to pain and a loss of function primarily in the knees and hips. It has been estimated that OA will represent the sixth leading cause of disability worldwide by 2020.[1] The 2010 Global Burden of Disease Study [2] showed that the overall prevalence of symptomatic knee OA was 3.8% higher in females than in males (means 4.8% and 2.8%, respectively). In terms of age, its prevalence reaches a peak at around 50 years of age. The same study classified knee and hip OA as the 11th highest contributor to global disability, accounting for 2.2% of years lived with disability. The following are the main known risk factors for developing knee OA: obesity, traumatic knee injury, misalignment, female gender, increasing age (especially between 50 and 75 years), occupational joint loading, and hand OA.[1, 3] Overweight or obese people have a 2.96 fold higher risk for the onset of knee OA than those with a normal Body Mass Index (BMI).[4] The most common symptom is pain, which is increased by mechanical stress, such as kneeling or lifting activities, and reduced by rest. Moreover, knee OA pain is also frequently associated with limited joint functionality and morning stiffness; these are partially recovered after movement. Treatment of knee OA includes both non-pharmacological measures, such as weight loss and physical therapy, and pharmacological measures. These include treatment with analgesic/anti-inflammatory drugs as well as symptomatic slow-acting drugs to treat OA; treatment is mainly focused on symptom relief and joint function preservation.[5] However, the main goal of OA therapy should be to delay cartilage degeneration and possibly to regenerate the cartilage structure.

Treatment with chondroprotectives is a valid approach in this sense. Chondroprotectives include glucosamine sulfate (GS), chondroitin sulfate (CS) and hyaluronic acid, important basic natural components of cartilage and synovial fluid. They are produced naturally by the body but these can be supplemented in the diet. In cases of articular cartilage damage, or less serious joint pathologies of traumatic origin, it has been observed that the combination of GS and CS can significantly reduce painful symptoms and improve joint function. This is achieved by improving cartilage metabolism and acting as a protective action so preventing any worsening of the disease.[6] This treatment has been shown to play a preventive role in the progression of OA itself, while the main focus of physiotherapy is to decrease pain; in effect, it acts on the symptoms, rather than the causes, of chondropathy.[7] In a recent study, 622 patients with knee OA were treated with CS once a day over a period of two years; the patients reported a rapid and enduring improvement in pain symptoms which was underlined by a significant reduction in the consumption of non-steroidal anti-inflammatory drugs during the study.[8] Recently, the effectiveness of another substance, curcumin, was identified as being able to reduce symptoms of rheumatoid arthritis. CartiJoint Forte, a dietary supplement, has recently become available. It contains CS, glucosamine hydrochloride (GH) and Bio-Curcumin BCM-95®, a *Curcuma longa* extract in high bioavailability titrated to 95% from curcuminoids, all substances known to have antioxidant properties.[9] It functions in maintaining joint function by promoting cartilage tropism.

The purpose of this study was to assess the efficacy of CartiJoint Forte, combined with physical therapy, as a treatment for subjects with knee OA. Given the proven validity of physical treatment for knee OA, it was hypothesized that its association with oral supplementation with CS, GH and curcumin would result in decreased pain, better functionality and improved mobility compared to exercise alone.

Materials and methods

A randomized, placebo-controlled study was performed by the Physical and Rehabilitation Medicine Departments of the Campus Bio-Medico University and Tor Vergata University, Rome, Italy.

Subjects were selected if they satisfied a variety of inclusion and exclusion criteria. They were required to be a minimum of 50 years old, have primary knee OA of the medial or lateral femorotibial compartment, meet the American College of Rheumatology classification criteria,[10] have disease severity Grade II or III on the Kellgren and Lawrence [11] classification (radiographic examination) and have suffered knee pain for a minimum of one month confirmed by a Visual Analogue Scale (VAS) score greater than 40 mm on a 100-mm scale.

Subjects were excluded if they had: a history or presence of rheumatic disease resulting in secondary OA, a history of traumatic knee lesions or actual injuries, previous knee surgery, a known or suspected allergy to

components in the investigational product or had taken oral, parenteral or intra-articular corticosteroids or infiltrative therapies in the previous three months. Further exclusions were made on general medical conditions, such as pregnancy, metabolic or oncological diseases, as well any condition that might confound the subsequent clinical evaluation of the outcomes.

Enrolled subjects were randomly assigned to one of two groups (experimental or control) using a randomization chart based on a stratification sequence for both age (under 65 *vs.* over 65 years) and gender (64% female proportion, to represent the greater prevalence of knee OA in the female population [1]). The method used was as follows: integer numbers, starting at 1, were assigned to subjects according to the stratification specification above, *i.e.* age and gender. Random numbers were generated by computer with each of them being successively paired with the integer numbers previously assigned. The random numbers were sorted in decreasing order. The subjects associated with the first half of the ordered random numbers, via their linked integer labels, were assigned to the experimental group. The remainder formed the control group.

The study was approved by the Ethics Committee of the Campus Bio-Medico University (Prot.: 63/12 PAR ComEt CBM). Prior to conducting the study-related procedures, each subject read and signed an informed consent form, as required in the World Medical Association Declaration of Helsinki.[12]

Therapy prescriptions

Subjects in both the experimental and control groups received two cycles of 10 one-hour physical therapy sessions, three times a week, each session being conducted under the supervision of experienced physiotherapists. During the first cycle, all the subjects performed a range of exercises. These included active and active-assisted mobilizations to recover the range of motion (ROM) of the hip, knee and ankle, stretching exercises of the quadriceps, hamstring, gastrocnemius and adductor muscles and exercises for strengthening the vastus medialis oblique muscle, first in supine position and subsequently in sitting posture.

During the second cycle, subjects performed isometric closed kinetic chain exercises (squat and semi-squat) and strengthening of adductors, abductors and rectus femoris muscles (flexing the hip against a progressive resistance starting with a one kilo weight on the thigh).

Throughout the whole study, the experimental group received two tablets of CartiJoint Forte per day, while the control group received two placebo tablets per day. In order to ensure the double-blind masking, the physiatrists who administered the tablets, were different from those who assessed the outcome measures. Both the physiotherapists and the subjects were blinded as to whether individual patients had been assigned to the experimental or control group in the trial. Compliance with study treatment was checked by providing the patients with a diary where they self-reported missing doses and by counting unused tablets at the end of the study period. The same diary also registered daily usage and doses of any rescue analgesia (restricted to paracetamol in 500-mg tablets).

Outcome assessment

After recruitment, individuals who met the eligibility criteria underwent an initial evaluation involving clinical and demographic information. The primary outcome for the trial was pain intensity measured by two VAS scores from 0 mm (no pain) to 100 mm (worst pain imaginable); one registered pain during normal daily living and the other pain when at rest. The secondary outcomes were measured using a number of instruments: knee function assessed by the Western Ontario and McMaster Universities Index for Osteoarthritis (WOMAC)[13], the Lequesne Index,[14] flexion and extension ROM, as well as inflammation assessment using C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) measurements. The WOMAC total score, designed to measure severity of knee OA, is calculated from responses to a self-administered questionnaire. It comprises three subscales: WOMAC pain (assessed by means of five questions), WOMAC stiffness (two questions), and WOMAC physical function (17 questions). Each question has a score that ranges from 0 to 10; higher scores represent greater pain, more stiffness, and worse knee function. The maximum WOMAC score is 240. The Lequesne Index contains eleven items, 5 related to pain, 2 related to the maximum distance walked and four related to daily activities. The maximum Lequesne Index score is 24, again with higher scores representing worse conditions. A questionnaire on lifestyle and eating behavior was administrated in order to evaluate any possible

changes during the trial. Finally, as a secondary objective, safety of the treatments was assessed by monitoring adverse events, both treatment-emergent and other, and by clinical evaluation. All measurements were recorded by physiatrists at baseline (T0), after 8 weeks (T1) and at the end of treatment after 12 weeks (T2), while CRP and ESR tests were performed at T0 and T2 checkpoints. All assessors were blinded to the subjects' assignments to the experimental or control groups.

Sample size calculation

The primary outcome variable, the VAS score, was assumed to have a Gaussian distribution and was based on an ordinal centesimal scale (0-100). Choosing an *a-priori* risk of alpha error equal to 0.05, it was possible to determine the appropriate sample size for each arm of the trial (treatment/control). A decrease in the perception of pain of 20% due to the treatment with nutraceutical supplement, with 26 patients in each group, represented an 85% power.

Statistical analysis

The main statistical measures were descriptive statistics such as the mean and standard deviation (SD) or the median with minimum and maximum values. In some instances relative frequencies with percentages were used to describe the behavior of parameters under consideration. Where required, normality of distributions was assessed using the Kolmogorov-Smirnov test. Where variables followed a normal distribution, one-way/two-

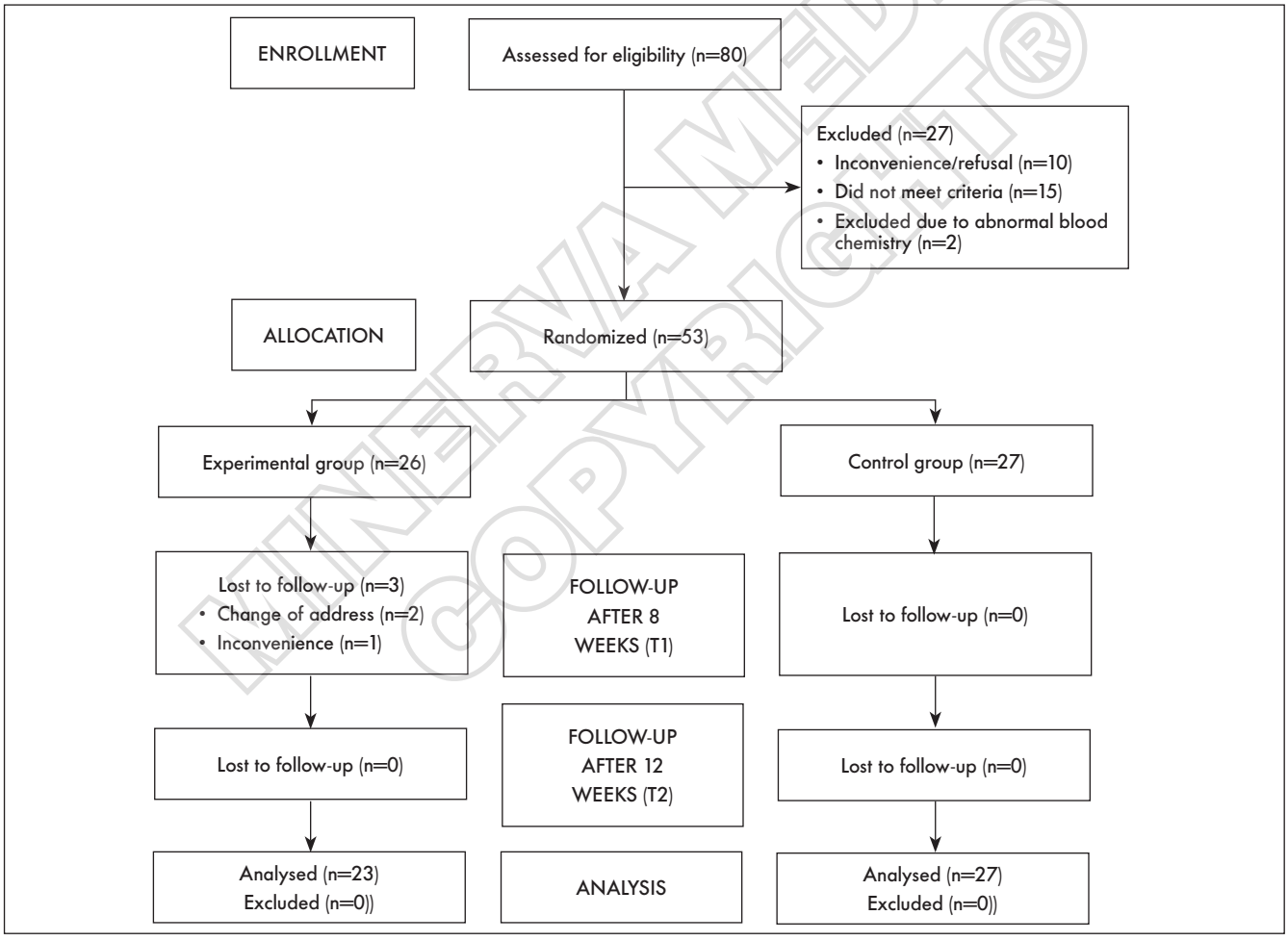

Figure 1.—Flow chart showing the number of subjects randomized and studied in each group.

way ANOVA or ANOVA for repeated measures were employed. The Kellgren-Lawrence grades had a non-normal distribution, so the non-parametric Kruskal-Wallis test was employed. χ^2 or Fisher's exact test (if cells sizes were below 5) were employed to testing dichotomous or categorical variables. Given the small sample size, when a statistically significant result was found, in order to check the robustness of the finding, the relative observed power (with alpha error = 0.05) was also computed. For all statistical analyses the level of significance was set at $P<0.05$.

The statistical software package, SPSS Statistics v.15.0 for Windows (IBM Corp., Chicago, IL, USA) was used to process data and perform tests and analyses.

Results

Sample characteristics

Fifty-three patients, previously diagnosed with OA, were enrolled onto the trial between January 2013 and July 2013; 26 were assigned to the experimental group and 27 to the control group. After enrolment, three subjects from the experimental group dropped out from the study (Figure 1); hence the experimental group size was reduced to 23 participants, representing an 83% power. Demographic and clinical characteristics were similar for both groups at the baseline assessment ($P>0.05$) (Table I). Compliance with the treatment required in the

TABLE I.—*Clinical and demographic characteristics of the sample at the baseline.*

Variables	Sample (N.=50)	CartiJoint group (N.=23)	Control group (N.=27)	P value
Gender				
Male	17 (34.0%)	9 (39.1%)	8 (29.6%)	0.480
Female	33 (66.0%)	14 (60.9%)	19 (70.4%)	
Age (years)	71.1±8.4	71.3±8.8	71.0±8.1	0.991
Weight (kg)	77.7±15.7	78.4±14.5	77.1±16.9	0.959
Height (cm)	162.9±9.0	164.4±9.6	161.7±8.5	0.402
BMI (kg/m²)	34.5±7.0	34.8±6.4	34.3±7.5	0.959
Education level				
Elementary	11 (22.0%)	4 (17.4%)	7 (25.9%)	0.814
Middle school	17 (34.0%)	9 (39.1%)	8 (29.6%)	
High school	19 (38.0%)	9 (39.1%)	10 (37.0%)	
University degree	3 (6.0%)	1 (4.3%)	2 (7.4%)	
Job				
Housewife	10 (20.0%)	6 (26.1%)	4 (14.8%)	0.418*
Employee	3 (6.0%)	2 (8.7%)	1 (3.7%)	
Retired	34 (68.0%)	15 (65.2%)	19 (70.4%)	
Craftsman	2 (4.0%)	0 (0.0%)	2 (7.4%)	
Other	1 (2.0%)	0 (0.0%)	1 (3.7%)	
Smoking habit				
No	44 (88.0%)	18 (78.3%)	26 (96.3%)	0.082*
Yes	6 (12.0%)	5 (21.7%)	1 (3.7%)	
Alcohol habit				
No	28 (56.0%)	13 (56.5%)	15 (55.6%)	0.945
Yes	22 (44.0%)	10 (43.5%)	12 (44.4%)	
Knee pain				
Right	20 (40.0%)	8 (34.8%)	12 (44.4%)	0.487
Left	30 (60.0%)	15 (65.2%)	15 (55.6%)	
Duration of disease (years)	7.0±6.7	6.8±7.6	7.2±6.0	0.837
Number of previous treatments	8 (16.0%)	4 (17.4%)	4 (14.8%)	0.578
Kellgren and Lawrence Grade	2.0 (2-4)	2.0 (2-4)	2.0 (2;4)	0.181**
VAS at rest	41.5±23.7	37.0±25.8	45.3±21.5	0.531
VAS on moving	63.8±17.9	65.7±21.1	62,2±14,8	0.499
Mean Global WOMAC Score	40.3±11.6	37.4±11.0	42.9±11.6	0.091
Lequesne Index	12.1±3.2	11.4±3.4	12.7±3.0	0.150
Use of walking aids	4 (8.0%)	2 (8.7%)	2 (7.4%)	0.867

Data are expressed as absolute number (%), mean ± SD, or median (range) (for non-normally distributed variables).
*Fisher's Exact Test; **Kruskal-Wallis test.
BMI: Body Mass Index; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

TABLE II.—*Differences of mean change of primary outcome measures within and between groups at T0, T1 and T2.*

Variables	CartiJoint group (N.=23)			Control group (N.=27)			P value			Observed power		
	T0	T1	T2	T0	T1	T2	Group	Check	Group × check	Group	Check	Group × check
VAS at rest	37.0±25.8	24.2±29.9*	14.6±17.3§	45.3±21.5	22.7±20.8*	22.6±18.5§	0.191	0.0001	0.458	–	–	–
VAS at motion	65.7±21.1	37.5±20.2*†	38.1±25.6§	62.2±14.8	51.9±21.1*	45.5±17.6§	0.045	0.0001	0.032	0.653	1.000	0.793

Data are expressed as mean ± SD. VAS: Visual Analogue Scale.
*P<0.05 (T1 *vs*. T0); §P<0.05 (T2 *vs*. T0); †P<0.05 (CartiJoint *vs*. control group).

TABLE III.—*Differences of mean change of secondary outcome measures within and between groups at T0, T1 and T2.*

Variables	CartiJoint group (N.=23)			Control group (N.=27)			P value			Observed power		
	T0	T1	T2	T0	T1	T2	Group	Check	Group × check	Group	Check	Group × check
WOMAC total score	37.4±11.0	26.5±13.3*	23.0±16.9§	42.9±11.6	28.7±13.7*	26.5±15.4§	0.099	0.0001	0.833	–	1.000	–
Lequesne Index	11.4±3.4	8.7±4.3*	7.9±3.5§†	12.7±3.0	10.2±3.5*	10.1±3.6§	0.009	0.0001	0.824	0.887	0.994	–
Knee extension ROM	4.7±5.1	3.8±5.6	4.1±5.5	7.7±5.6	5.2±5.5	4.7±5.8	0.067	0.194	0.557	–	–	–
Knee flexion ROM	106.1±10.7	110.5±10.8	110.4±8.4	105.6±16.6	109.7±12.3	109.5±9.6	0.693	0.133	0.996	–	–	–
CRP test	3.1±3.2	N/A	4.2±4.4	4.6±4.7	N/A	4.2±4.2	0.369	0.374	0.995	–	–	–
ESR test	33.9±20.5	N/A	36.5±25.3	40.8±27.9	N/A	40.7±25.4	0.096	0.815	0.776	–	–	–

Data are expressed as absolute count plus percentage (between brackets) or mean ± SD.
WOMAC: Western Ontario and McMaster Universities Index for Osteoarthritis; ROM: range of motion; N/A; not assessed; CPR: C-reactive protein; ESR: erythrocyte sedimentation rate.
*P<0.05 (T1 *vs*. T0); §P<0.05 (T2 *vs*. T0); †P<0.05 (CartiJoint *vs*. control group).

study was excellent; the number of patients reporting over 90% drug/placebo intake during the study period ranged from 89% to 97%, with no significant difference between the groups.

Primary outcome

As a primary outcome, we assessed the effect of CartiJoint Forte, supplemented with a physical training program, on knee pain, by means of VAS scores recorded under two different conditions (Table II). For the VAS at rest, we found no interaction 'group x time-check' (F=0.785; P=0.458). However, a within-groups statistically significant reduction between T1 *vs*. T0 and T2 *vs*. T0 (F=13.712; P=0.0001) emerged, although no differences were found in the comparison between groups (F=1.724; P=0.191). Neither group showed a similar reduction of rest pain at times T1 and T2 compared to that recorded at baseline (T0), providing no evidence of changes between half-treatment evaluation and at end of the treatment. In relation to the VAS on moving scores, a test using repeated measures ANOVA revealed a significant "group × time-check" interaction (F=2.491; P=0.032), which underpins an increasing effect of time on VAS score reduction (F=17.748; P=0.0001) for both groups. There was however a substantial inter-groups difference, especially at the T1 check (F=3.437; P=0.045). Indeed, after 8 weeks of treatment, knee pain at motion for the experimental group appeared to be significantly reduced compared to the control group.

Secondary outcomes

In order to assess the effect of nutraceutical supplementation on functional status, and, consequently on daily life performance, a series of parameters were investigated using some widely used evaluation tools (Table III). First, the WOMAC Index was been measured. As described above, higher scores are associated with worse functional status (including joint pain and stiffness). An analysis of variance test of the WOMAC score showed a statistically significant reduction, independent of groups (F=2.751; P=0.099), between check 1 *vs.* check 0 and check 2 *vs.* check 0 (F=17.463; P=0.0001). No relevant differences were found between T2 and T1, in either group.

Similarly, with the Lequesne Index, an ANOVA test showed a statistically significant decrease observed between check 1 and check 0, and between check 2 and check 0 (F=9.535; P=0.0001), but without any significant change from T1 to T2.

TABLE IV.—*Differences in caloric intake, weight and BMI at the baseline (T0) and final (T2) assessment.*

Variables	CartiJoint group (N.=23)		Control group (N.=27)		P value (between groups)
	T0	T2	T0	T2	
Kcal/die	2087.1±317.7	2065.3±345.7	2107.4±344.0	2109±325.9	0.880
Weight (kg)	78.4±14.5	79.1±14.6	77.1±16.9	77.0±16.6	0.907
BMI (kg/m²)	34.8±6.4	34.0±9.7	34.3±7.5	34.2±7.4	0.880

Data are expressed as mean ± SD. BMI: Body Mass Index.

However, a group effect was identified; the experimental group showed a lower score at the T2 check compared to the placebo group (F=7.091; P=0.009). Assessment of knee ROM did not show any intra or inter-groups differences either with flexion (F=0.004; P=0.996) or extension (F=0.588; P=0.557). Finally, neither ESR and CRP tests revealed any significant changes after therapy; between groups "group × time-check" interaction ANOVA results were CRP (F=0.000; P=0.995) and ERS (F=0.082; P=0.776).

Questionnaire on lifestyle and eating behaviors

No statistically significant differences for calorie intake, weight or BMI, before and after treatment, were found in either group (Table IV).

Adverse effects (AE)

No adverse events were reported during the study.

Discussion

In developed countries there is an increasing interest in using natural remedies, particularly those of botanical origin, for the treatment of chronic OA pain. This randomized placebo-controlled study was performed to evaluate, for the first time, if an integrated approach based on oral intake of Bio-Curcumin with GH and CS, accompanied by a physical exercise program, could reduce pain symptoms and improve knee function in patients with primary knee OA. In the literature, several combinations of pharmacological and non-pharmacological approaches for treating knee OA may be found. However, treatment is traditionally based on each individual patient's assessment, taking into account their needs and preferences.[15] In the pharmacological part of the knee OA treatment, glucosamine and chondroitin represent a non-negligible time, since the beginning, due to their benefits on joint structure among patients with mild to moderate disease.[16] Apart from their efficacy, both glucosamine and chondroitin are safe medications with no difference in their adverse effects compared to a placebo.[17]

Bio-molecular studies have shown that the combination of glucosamine and chondroitin suppresses IL-1-induced gene expression of iNOS, COX-2, mPGEs and NF-kB in cartilage explants.[18] This leads to reduced production of NO and PGE2, two mediators responsible for cell death of chondrocytes and inflammatory reactions.[19] In comparison to glucosamine and chondroitin, hyaluronic acid has a minor anti-inflammatory and anti-apoptotic effect.[20] In previous randomized controlled studies the effectiveness of the association of glucosamine and chondroitin in knee OA was evaluated, and this combination proved more effective than a placebo in attenuating pain and joint rigidity.[21] This benefit was evident in patients with mild-to-moderate disease but was not demonstrated in those with severe conditions.[22]

Curcumin offers considerable potential as an aid in preventing, or at least delaying, the onset of OA. Curcumin and its derivatives are part of the curcuminoids family, being derived from *Curcuma longa* L. or turmeric. Curcumin is recognized as being able to suppress gene expression of matrix metalloproteinases,[23] which are destructive enzymes that can dissolve cartilage structure.[24] Moreover, it can block inflammatory signaling molecules (multiple cytokine IL-1β), that aggravate painful joint inflammation.[25] Laboratory studies show that curcumin slows cartilage IL-1β induced degeneration by restoring normal production of proteins of the cartilage.[26, 27] Hence, it might be a beneficial addition to the conventional drug regimen in OA treatment.

In the present study, a significant improvement was found VAS scores at motion for each study group at both 8 and 12 weeks; further, the experimental group showed a more consistent reduction in pain after eight weeks of treatment, probably due to the effect of the

nutraceutical supplementation demonstrating its full effect. At the end of the study period, no between-groups differences were observed, likely due to a plateau effect for the CartiJoint Forte. Similarly, with respect to the algofunctional Lequesne Index, this study revealed an improvement at the end of the study for both groups; however, treated patients had better scores compared to the controls. WOMAC global scores exhibited an ameliorating trend across all study time-points, without any discrepancy between groups.

The results from this trial are in line with those found in the literature. In a recent randomized, double-blind, placebo-controlled study, Nakagawa *et al.*[28] reported a trial with 50 knee OA patients, with Kellgren-Lawrence grade II or III, where a significant reduction in pain was observed after an 8 week administration of a surface-controlled water-dispersible form of curcumin. The authors also observed a more pronounced lowering of celecoxib dependence in the group of patients treated with curcumin than in the placebo group. Panahi *et al.*[29] conducted a pilot randomized double-blind placebo-controlled parallel-group clinical trial among 19 patients with mild to moderate knee OA. They were assigned either 1500 mg/day curcuminoids or a placebo for 6 weeks. By analyzing changes in WOMAC, VAS and Lequesne Index scores, they concluded that curcuminoids represent an effective and safe alternative treatment for OA. The results from our trial are substantially consistent with these findings, although less pronounced. This may be the result of the beneficial effect of physical therapy, which was provided to both experimental and control subjects.

Kuptniratsaikul *et al*.,[30] in a multicenter research study on 367 primary knee OA patients, compared the efficacy and safety of *Curcuma domestica* extracts to ibuprofen. They concluded that *Curcuma domestica* extracts are as effective as ibuprofen in the treatment of knee OA; they noted a similar side effect profile in both groups but with fewer gastrointestinal AE reports for the *Curcuma domestica* extracts group. By contrast, Pinsorsnak *et al*.,[31] in a double-blind placebo-controlled parallel-groups trial, found no significant difference in VAS scores after 3 months of treatment with diclofenac 75 mg/d plus curcumin 1000 mg/d in a cohort of 37 over-50 year old patients with mild to moderate knee OA, compared to diclofenac plus placebo in 36 age-matched knee OA subjects.

Provenza *et al.*[32] observed that combined GS and CS, once or three times daily, provided appropriate analgesia in knee OA, independent of dose level and whether in capsule or sachet formulation. The findings stated above seem to contradict those of the study by Messier *et al*.,[33] on a sample of 89 older adults suffering from knee OA. They found no difference in VAS score and WOMAC function for a one-year treatment using 1500/1200 mg/d GH/CS accompanied by up to 6 months of physical therapy compared to placebo plus exercise. The long-lasting treatment period could account for these results; indeed, a meta-analysis suggests that glycosaminoglycans have a short-term effect on pain relief.[34] However, another review supports its structural and symptomatic efficacy.[35] A recent meta-analysis by Wu *et al.*[36] examined 19 randomized clinical trials involving an overall sample size of 3159 knee/hip OA patients; in comparing the efficacy of different preparations of glucosamine (sulfate and hydrochloride) for pain reduction and physical function against placebo, it concluded no efficacy for glucosamine in reducing pain and only a mild effect in improving physical function, as evaluated by the Lequesne Index.

Our study did not identify differences between and within groups with respect to ROM assessment, probably due to the fact that at the baseline assessment subjects showed an almost full knee ROM. Finally, when comparing ESR and CRP test values before and after treatment, no differences were found in either group; these results may be due to the older average age of our sample and so may be influenced by possible comorbidities.

Several studies suggest that pain relief and improvement of joint function in patients with knee OA may be attributable to weight loss.[37, 38] In our study no difference in BMI was found between the baseline and final assessments; therefore, this finding could confirm the validity of the results of our study.

Throughout the study, no adverse side effects were observed that could be attributed to the intake of Bio-Curcumin with GH, CS. This finding confirms numerous literature reports of the good safety profile of biocurcumin, GH and CS although it diverges from the Kuptniratsaikul *et al.*[30] study of 185 patients suffering from knee OA that found a 29.7% occurrence of adverse events in a treatment with *Curcuma domestica* extracts. The majority of the side effects were related to the gastro-enteric tract, for example dyspepsia, abdominal pain/distension and nausea. A possible explanation for

this discrepancy lies in the different rescue medications administered for the relief of severe pain; the patients in the above-mentioned study took tramadol while only acetaminophen was permitted in the present study.

Some limitations to the current study need to be noted. It lacks a follow up evaluation, for example to check for possible long-lasting effects of the treatment beyond the 3-month duration of the trial, perhaps at 6 and/or 12 months.

This was the time frame suggested for glycosaminoglycans.[39] Indeed, recently it has been shown that some components of glycosaminoglycans (also known as Symptomatic Slow Acting Disease Drugs for Osteoarthritis), when prescribed over a long time period, present disease modifying potential as measured by joint space narrowing on X-ray or nuclear magnetic resonance imaging.[40] This suggests another limitation of the present study; although the enrolled patients were evaluated using an X-ray examination of their knees at the baseline, there was no further radiographic examination during the study. Hence, it has not been possible to objectively quantify the disease-modifying potential of the nutraceutical treatment on knee OA.

Conclusions

Our preliminary results show that treatment with Bio-Curcumin BCM-95® with GH and CS, accompanied by physical therapy, may improve pain symptoms during the activities of daily living and reduce algofunctional Lequesne Index values in mild to moderate knee OA patients.

Although the validity of the findings in the trial is limited by the sample size, the results provide preliminary evidence of the usefulness of CartiJoint Forte in knee OA management. Further research along a number of paths is warranted. Possible extensions include using a longer follow-up period in order to assess the optimal duration of treatment as well as expansion to other populations, for example, to determine if it could be a therapeutic treatment for sufferers of hip OA.

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Conflicts of interest.—I. Panni is a clinical project manager at Fidia Farmaceutici S.p.A., which owns the rights to CartiJoint (trademark application no. 008952087).

Acknowledgements.—The authors wish to thank Sandra Miccinilli, Marco Del Duca, Manuela Mori and Antonella Migliorino for their help in collecting and organizing the data, as well as Roberto P. Sorge and Maria C. Buè for their contribution to the data analysis and presentation. Fidia Farmaceutici S.p.A. provided Nutraceutical supplies to the study on a non-profit study basis.

Article first published online: March 3, 2016. - Manuscript accepted: March 1, 2016. - Manuscript revised: January 8, 2016. - Manuscript received: January 12, 2015.