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# Effect of the Novel Low Molecular Weight Hydrolyzed Chicken Sternal Cartilage Extract, BioCell Collagen, on Improving Osteoarthritis-Related Symptoms: A Randomized, Double-Blind, Placebo-Controlled Trial

Alexander G. Schauss,[†] Jerome Stenehjem,[§] Joosang Park,*[,#] John R. Endres,[†] and Amy Clewell[‡]

[†]AIBMR Life Sciences, Inc., 4117 South Meridian, Puyallup, Washington 98373, United States

[§]Division of Trauma, Surgical Critical Care & Burns, School of Medicine, University of California at San Diego, 2999 Health Center Drive, San Diego, California 92123, United States

[#]BioCell Technology, LLC, 11th Floor, 4695 MacArthur Court, Newport Beach, California 92660, United States

[‡]AIBMR Life Sciences, Inc., Suite 106, 120 West Seventh Street, Bloomington, Indiana 47404, United States

**ABSTRACT:** Osteoarthritis (OA) is a significant source of pain and disability. Current medical and surgical treatments can be costly and have serious side effects. The aim of this randomized, double-blind, placebo-controlled trial was to investigate the tolerability and efficacy of BioCell Collagen (BCC), a low molecular weight dietary supplement consisting of hydrolyzed chicken sternal cartilage extract, in the treatment of OA symptoms. Patients ($n$ = 80) in the study had physician-verified evidence of progressive OA in their hip and/or knee joint. Joint pain had been present for 3 months or longer at enrollment, and pain levels were 4 or higher at baseline as assessed by Physician Global Assessment scores. Subjects were divided into two groups and administered either 2 g of BCC or placebo for 70 days. Other outcome measurements included visual analogue scale (VAS) for pain and Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores taken on days 1, 35, and 70. The tolerability profile of the treatment group was comparable to that of the placebo. Intent-to-treat analysis showed that the treatment group, as compared to placebo, had a significant reduction of VAS pain on day 70 ($p < 0.001$) and of WOMAC scores on both days 35 ($p = 0.017$) and 70 ($p < 0.001$). The BCC group experienced a significant improvement in physical activities compared to the placebo group on days 35 ($p = 0.007$) and 70 ($p < 0.001$). BCC was well tolerated and found to be effective in managing OA-associated symptoms over the study period, thereby improving patient's activities of daily living. BCC can be considered a potential complement to current OA therapies.

**KEYWORDS:** *hydrolyzed chicken sternal cartilage extract, hydrolyzed collagen type II, biocell, osteoarthritis, WOMAC, joint line tenderness and pain, activities of daily living, alternative medicine*

## INTRODUCTION

Osteoarthritis (OA) is a degenerative disease of the joints, which involves progressive deterioration of the articular cartilage. It is the most common form of arthritis, affecting >10% of the U.S. population.[1] This chronic joint condition, more common in women, usually starts between the ages of 50 and 60 and is the leading cause of disability in those over the age of 65.

The etiology of OA is unknown. However, obesity, aging, trauma, repetitive strenuous joint activity, and genetics are risk factors associated with the development of the disease. The progression of OA results in disability due to joint pain, stiffness, and swelling in the knees, hips, hands, and spine. The molecular pathogenesis of OA appears to involve complex interactions among multiple pathways leading to the loss of structural components, including collagen type II and glycosaminoglycans (GAGs) such as chondroitin sulfate and hyaluronic acid (HA), and to inflammation and senescence of chondrocytes.[2]

Because there is no cure, treatment of OA aims to control progression of disease, to control pain, to improve or maintain range of movement, and ultimately to improve or maintain function. Pharmaceutical regimens involve analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) to alleviate pain. However, these interventions provide only partial symptomatic relief and are not believed to affect underlying disease progression. NSAID therapy is also associated with gastrointestinal and cardiovascular complications.[3,4] Intra-articular injection of HA is practiced by clinicians, but considered costly, its clinical effects often being temporal and its benefits controversial.[5]

In an effort to discover active compounds that are safe, efficacious, and cost-effective in managing OA symptoms, some dietary supplements including glucosamine, chondroitin, vitamin D, and polyunsaturated fatty acids have been evaluated in clinical trials. Many of these trials have demonstrated that these supplements might help reduce joint pain and in some cases favorably affect structural changes.[6−8]

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Currently, among all dietary supplements indicated for OA-associated symptoms, a combination of glucosamine and chondroitin sulfate is most commonly used. However, recent studies have cast doubt on the efficacy of these agents. The NIH-funded glucosamine/chondroitin arthritis intervention trial (GAIT) failed to find statistically significant efficacy in preventing radiological progression of OA of the knee, although a subgroup analysis showed small to moderate efficacy for a segmented group of patients with a moderate to severe degree of pain.[8,9] A recent meta-analysis of 10 well-designed human trials demonstrated that supplementation with glucosamine (>800 mg) and chondroitin sulfate (>1500 mg) had no greater efficacy than placebo in relieving pain or in influencing joint space width in 3803 subjects suffering from OA of the knee or hip joint.[10] In addition, oral supplementation with GAGs only appears to overlook the fact that cartilage extracellular matrix is a highly organized collagen fibrillar network embedded with proteoglycans (PGs), which consist of a noncollagenous core and link proteins as well as GAGs such as chondroitin sulfate and HA.[11]

There is growing interest in hydrolyzed collagen (or collagen hydrolysate) as a nutraceutical supplement because collagen-derived (poly)peptides harbor a variety of interesting biological properties. First, hydrolyzed collagen [as opposed to undenatured (unhydrolyzed) collagen] derived from bovine collagen type I or chicken sternal cartilage collagen type II has been shown to stimulate chondrocytes in vitro to produce type II collagen and PGs.[12,13] Second, orally administered radiolabeled hydrolyzed collagen has been shown to deposit into the articular cartilage in mice.[14] In addition, ingestion of hydrolysates derived from chicken sternal cartilage or porcine skin led to the presence of various di- and tripeptides in human serum and plasma including proline−hydroxyproline (Pro-Hyp) dipeptide as the major form.[15] Interestingly, orally administered Pro-Hyp dipeptides in C57BL/6J mice inhibited the loss of chondrocytes and thinning of the articular cartilage caused by phosphorus-induced degradation, suggesting that hydrolyzed collagen-derived Pro-Hyp may signal chondrocyte differentiation, leading to cartilage protection in stressed conditions.[16] These results raise the intriguing possibility that hydrolyzed collagen may have a potential to repair or regenerate deteriorating cartilage. Earlier clinical trials, reviewed by Bello and Oesser, displayed the safety and promising effects of hydrolyzed collagen in managing symptoms associated with OA or other arthritic conditions.[13] A recent clinical trial evaluating the effect of the daily intake of 10 g of hydrolyzed collagen for 6 months in 250 OA patients showed that hydrolyzed collagen was safe and effective in reducing VAS and WOMAC pain scores, although not effective in reducing total WOMAC score.[17]

The hypothesis of how hydrolyzed collagen may reduce OA-associated symptoms includes providing bioavailable substrate (building blocks) for the collagen fibrillar network, which provides tensile strength for the matrix of articular cartilage. Hydrolyzed collagen, used for the majority of clinical trials, contains primarily type I and III collagen derived from bovine or porcine skin sources. However, the articular cartilage (and collagen network) is comprised predominantly of type II collagen embedded with PGs such as aggrecans—a multimolecular complex composed of chondroitin sulfate, HA, and noncollagenous core/link proteins. PGs are essential for the resistance of cartilage against compressive and shearing loading forces. HA plays an additional role as a major lubricating agent of the synovial fluid in the joint.[11] As the loss or the breakdown of both collagen and GAG components is implicated in the progression of OA, supplementing their building blocks with cartilage-derived substances (type II collagen) could be a better approach than providing either hydrolyzed collagen type I/III or GAG precursors.

BioCell Collagen (BCC) is derived from chicken sternal articular cartilage. It is a proprietary nutraceutical grade powder composed of a soluble naturally occurring matrix of hydrolyzed collagen type II, chondroitin sulfate, and HA. The composition is similar to that of the human articular cartilage lining found in the synovial joints. To investigate its tolerability and efficacy, a randomized, double-blind, placebo-controlled study was conducted in 80 OA patients who were suffering from a moderate to severe degree of disease-associated symptoms in their hips and/or knee joints.

## MATERIALS AND METHODS

**Study Design.** This trial was conducted at multiple hospital sites and managed by a professional contract research organization in accordance with Good Clinical Practice and ICH guidelines. The protocol was reviewed and approved by an Institutional Review Board/Independent Ethics Committee at each site. A total of 80 patients were enrolled and randomly distributed between BCC ($n$ = 40) and placebo ($n$ = 40) groups. Table 1 shows the study design for the trial, which lasted for 70 days.

**Table 1. Study Design**

| procedure | visit 1, day 0 | visit 2, day 35 | visit 3, day 70 |
|---|---|---|---|
| obtain informed consent | x | | |
| evaluation of inclusion/exclusion criteria | x | | |
| relevant medical history | x | | |
| assignment/randomization of subject numbers | x | | |
| general clinical examination with systemic examination | x | x | x |
| completion of VAS scale | x | x | x |
| completion of WOMAC | x | x | x |
| dispersal of investigational product | x | x | |
| dispersal of Paracetamol | x | x | |
| dispersal of patient diary | x | x | |
| gather adverse event reports | | x | x |
| recovery of patient diary | | x | x |
| recovery of investigational product | | x | x |

Informed consent was obtained from each subject on initial contact. Male/female subjects aged 40−70 years who showed clinical evidence of OA based on a physician's examination of hip and/or knee joints were enrolled. The trial was designed to evaluate the effect of BCC in relieving symptoms in patients with progressive OA. Inclusion criteria included OA patients who had a pain level of ≥4 on a VAS scale of 0−10 and pain present for a duration of 3 months or longer and at least 5 of 7 days a week. Exclusion criteria included a history of serious or chronic medical conditions including diabetes, liver diseases, psychiatric disorders, pregnant and lactating females, those with a history of rheumatoid arthritis or any other inflammatory arthritis, and those under NSAID treatment for the past 15 days or alternative treatment for OA except acetaminophen taken as Paracetamol (McNeil Consumer Healthcare, Fort Washington, PA). At the time of enrollment, four in the placebo and six subjects in the BCC group had taken pain and anti-inflammatory drugs and injections, which included Paracetamol, Diclofenac, Nimulid, and Depomedrol.

**Test Article.** The dietary ingredient used in the study was BioCell Collagen (BioCell Technology, Newport Beach, CA, USA), a


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hydrolyzed chicken sternal cartilage extract composed of a naturally occurring matrix of hydrolyzed collagen type II (~1.5−2.5 kDa) and low molecular weight chondroitin sulfate and HA. Each capsule contained 500 mg of BCC providing a naturally occurring composition of hydrolyzed collagen type II (300 mg), depolymerized chondroitin sulfate (100 mg), and hyaluronic acid (50 mg). Uncharacterized components of sternal cartilage account for the remaining 50 mg. The placebo capsule contained 500 mg of inert cellulose and was indistinguishable from the BCC capsule upon examination by blinded inspectors. Each subject was instructed to take two capsules (1 g) of BCC or placebo in the morning and two capsules in the evening. A 2 g daily dose of BCC was shown to be well-tolerated by OA patients enrolled in a previous unpublished pilot clinical trial study. Of 80 enrolled subjects, 68 subjects (35 in the BCC group, 33 in the placebo group) completed all three visits. Subjects who failed to complete the study included 3 in the placebo group due to voluntary withdrawal from the study, 1 in the BCC group due to an adverse event, and 8 subjects (4 per group) who were lost to follow-up. The BCC group had 3 and the placebo group had 5 subjects who deviated from the protocol. All of the violations except for one in the placebo group were considered to be minor, either missing several doses or visiting one to three days outside the window period for the scheduled visits on days 35 and 70. All 80 enrolled subjects were included for the intent-to-treat statistical analysis. Data unavailable due to the failure of follow-up visits were imputed from data at the prior visit.

NSAIDs, corticosteroids (oral route or injectable), and drugs causing central nervous system depression were forbidden during the study duration. Subjects were not allowed to take any analgesic other than Paracetamol (acetaminophen). The consumption of Paracetamol was recorded in corresponding patient diaries dispensed at each previous visit. A maximum of 4 g of Paracetamol could be taken in a day. Subjects were allowed to continue on concomitant medication deemed not to affect the outcome of this study.

**Randomization and Blinding.** Subjects were randomized to one of the two treatment groups using seed 7422 computer validated software (www.randomization.com). Investigators received blinded sealed envelopes corresponding to the treatments that were dispensed to subjects. An envelope could be opened in case of an emergency (serious adverse events) and only if knowledge of the product was necessary to start proper therapy. None of the sites opened the coded envelopes until the end of the study because there were no serious adverse events.

**Outcome Measures.** The tolerability and efficacy outcome evaluations used in this study are standard for OA clinical trials due to their reliability and relevance.

All subjects were informed at the beginning of the study that they must contact the investigator in the event of any perceived side effect during the period of their participation in the study. The seriousness of adverse events was graded by the investigator as described in the protocol, using a three-point intensity scale: (1) mild, awareness of signs or symptoms, but easily tolerated; (2) moderate, uncomfortable enough to cause interference with usual activity; (3) severe, incapacity with inability to work or do usual activity. Adverse or intercurrent events were discovered during the history-taking and clinical examination or spontaneously reported by the subject at each visit and recorded in the Case Report Form, which described the nature (diagnosis, signs, and symptoms), severity, date/time of end, outcome, and actions taken. The relationship to study treatment and seriousness of any reported adverse event was based on the investigator's opinion.

Investigators clinically assessed subjects on all three visits (days 1, 35, and 70). The Physician Global Assessment (VAS) was conducted by a physician to measure the degree of tolerability of the treatment as well as its efficacy. The VAS has superior test−retest reliability as shown to be valid, reliable, and sensitive to change in patients with OA of the hip and/or knee.[18] As described below, this study also incorporated WOMAC scores as a main outcome measure. Employing both VAS and WOMAC (Likert version) measures for our study is also supported by the Bolognese et al. study that showed VAS and Likert responses were highly correlated and displayed similar accuracy in distinguishing treatments in OA patients.[19]

A pain evaluation and clinical examination was performed at each visit. Pain was measured using the VAS scale, measured to the nearest 0.5 cm, and recorded as the pain score. The WOMAC Osteoarthritis Index, a validated 24-item symptom assessment research tool, was used to assess knee and hip OA symptoms. Pain, disability, and joint stiffness are assessed with 5, 17, and 2 items, respectively. The WOMAC is rated on an ordinal scale of 0−4, with lower scores indicating a lower level of symptoms or physical disability. Each subscale is summed to a maximum score of 20, 68, and 8, respectively. There is also a global score, which is calculated by summing the scores for the three dimensions.

**Statistical Analysis.** Analysis of variance (ANOVA) or non-parametric equivalent of ANOVA was used for analysis. Comparisons between the BCC and the placebo groups were made on days 35 and 70 using variance analysis with the baseline values on day 0 as a covariate. Probability ($p$) values lower than 0.05 were considered to be statistically significant.

## RESULTS

**Baseline Characteristics.** Demographics and baseline characteristics of patients are summarized in Table 2. Overall, baseline characteristics between the groups were similar with regard to age and past medical treatment for OA. However, gender ratio and percentage of hypertension varied slightly between the groups.

**Table 2. Demographic and Baseline Characteristics of the Subjects**

| | BioCell Collagen | placebo |
|---|---|---|
| no. of subjects enrolled | 40 | 40 |
| no. of subjects completed | 35 (87.5%) | 33 (82.5%) |
| av age (years) | 54.3 ± 8.69 (SD) | 54.5 ± 9.79 (SD) |
| male/female (female %) | 12:23 (66%) | 15:18 (55%) |
| prior medical treatment | | |
| related to osteoarthritis | 4/35 (11%) | 4/33 (12%) |
| unrelated-hypertension[a] | 4/35 (11%) | 2/33 (6.1%) |

[a]The subjects were allowed to take proper medication throughout the study.

**Treatment Compliance.** Compliance was defined by the percentage of assigned doses that were actually consumed, as determined by pill counts on day 35 and 70 visits. Overall, there was 98.7% compliance in the BCC group and 100% in the placebo group, and there was no statistically significant difference in compliance rate between the two groups ($p$ = 0.294).

**VAS Score.** Figure 1a plots changes in VAS scores at days 35 and 70 from baseline. Whereas both BCC and placebo groups experienced a significant reduction in VAS scores on days 35 and 70 ($p < 0.001$, for each group), the BCC group showed a greater reduction of scores (18.9 vs 13.4% on day 35 and 32.0 vs 14.9% on day 70). This difference was statistically significant on day 70 ($p < 0.001$). Figure 1b shows that 3 (7.5% on day 35) and 14 (35% on day 70) of 40 subjects in the BCC group had a decrease in VAS pain score by at least 30 mm, whereas none (day 35) and only 1 (2.5% on day 70) subject in the placebo group had the same degree of pain reduction.

**WOMAC Score.** The WOMAC Index score is calculated by summing three components: pain, stiffness, and disability. Table 3 shows changes in WOMAC and its subscores at days 35 and 70 from baseline. Although both groups had a significant reduction in WOMAC scores on days 35 and 70 ($p < 0.001$ for both groups), the BCC group showed a greater reduction of WOMAC score both on days 35 and 70 than the


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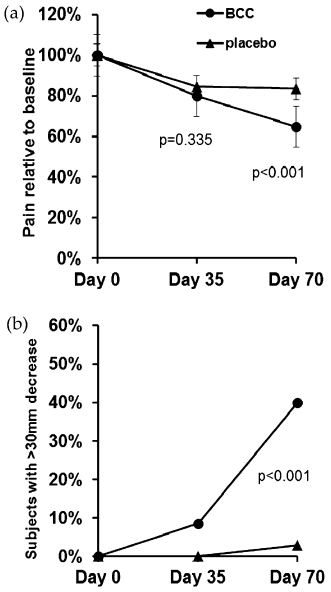


**Figure 1.** Effect of daily supplementation with BioCell Collagen on VAS pain score compared to placebo: (a) baseline-adjusted VAS scores on days 35 and 70 in each treatment group (the $p$ values of the group differences are shown); (b) comparison of the percentage of subjects in each treatment group who experienced a decrease in VAS pain score by at least 30 mm on days 35 and 70, as compared to the baseline score on day 0.

placebo. This difference was significant on both days ($p = 0.017$ on day 35; $p < 0.001$ on day 70).

The WOMAC subscores of pain, stiffness, and physical difficulties were compared between the groups. First, the BCC group, as compared to placebo, had a larger degree of pain reduction, and the mean difference on day 70 was close to statistical significance ($p = 0.052$). Second, the mean difference in stiffness between the groups was not statistically significant on day 70 ($p = 0.081$). Third, the mean difference in difficulty of physical activities was significant on both days ($p = 0.007$ on day 35 and $p < 0.001$ on day 70). The analysis of the WOMAC (sub)scores suggested that BCC was significantly more effective than placebo in reducing the WOMAC score, particularly in reducing difficulty in performing various physical activities.

**Adverse Events.** Table 4 summarizes adverse events that occurred during the 70-day trial period. There were no severe adverse events reported from either group. The BCC group had one mild (probably related to BCC) and two moderate (unrelated) adverse events, all of which resolved. The placebo group had five mild (two possibly related and three unrelated to the placebo) and one moderate (unrelated) adverse events. Except for the moderate adverse event of high blood pressure, all adverse events were successfully treated. Thus, there was no significant difference between the two groups in the total number of adverse events ($p = 0.242$) and in the total number of subjects who had adverse events ($p = 0.940$).

**Rescue Medication Use.** When average daily use of Paracetamol between the first day and on day 35 was compared, a greater percentage (15/35, 45.5%) of subjects on BCC reduced their use of the rescue medication as compared to those on placebo (11/33, 33.3%). Furthermore, 17 of 33 subjects (51.5%) on placebo increased Paracetamol usage, whereas only 12 of 33 (36.4%) on BCC increased its usage.

## DISCUSSION

This study demonstrated that 1 g of BCC twice daily was well tolerated on the basis of the comparable number of adverse reactions seen between treatment and placebo groups. The efficacy measurements used in the current trial showed that BCC was effective in reducing VAS-reported pain and improving physical function in treated subjects. The WOMAC Index further supported the greater improvement in symptoms such as physical disability, as the trial proceeded. The reduction of pain measured by WOMAC in the BCC group was also larger than in the placebo group, but the difference was not significant on day 70 ($p = 0.052$). Given the trend toward statistical significance, it would be interesting to investigate whether a longer term study would lead to significant WOMAC pain reduction.

In this trial, the study subjects had a progressive state of OA prior to enrollment, with VAS pain scores ranging from 4 to 9.2

**Table 3. Effect of Daily Supplementation with BioCell Collagen on WOMAC (Sub)score**

| outcome variable | placebo | $p$ value[a] | BioCell Collagen | $p$ value[a] | $p$ value[b] |
|---|---|---|---|---|---|
| WOMAC score | | | | | |
| day 0 | 54.87 ± 10.11 | | 54.55 ± 11.54 | | 0.555 |
| day 35 | 47.11 ± 11.78 | 0.004 | 42.08 ± 12.37 | <0.001 | 0.017 |
| day 70 | 44.03 ± 13.81 | <0.001 | 33.77 ± 11.56 | <0.001 | <0.001 |
| WOMAC subscore | | | | | |
| pain | | | | | |
| day 0 | 10.53 ± 2.71 | | 9.88 ± 2.93 | | 0.726 |
| day 35 | 8.18 ± 2.23 | <0.001 | 7.55 ± 2.55 | <0.001 | 0.332 |
| day 70 | 7.48 ± 3.40 | <0.001 | 6.13 ± 2.66 | <0.001 | 0.052 |
| stiffness | | | | | |
| day 0 | 4.28 ± 1.34 | | 4.30 ± 1.36 | | 0.936 |
| day 35 | 3.43 ± 1.48 | 0.007 | 3.25 ± 1.48 | 0.001 | 0.739 |
| day 70 | 3.00 ± 1.68 | <0.001 | 2.48 ± 1.15 | <0.001 | 0.081 |
| physical difficulties | | | | | |
| day 0 | 39.20 ± 8.75 | | 40.35 ± 8.51 | | 0.897 |
| day 35 | 36.13 ± 8.97 | 0.121 | 31.90 ± 8.88 | <0.001 | 0.007 |
| day 70 | 32.90 ± 10.03 | 0.003 | 26.65 ± 8.62 | <0.001 | <0.001 |

[a] $p$ value for intragroup difference. [b] $p$ value for intergroup difference.


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**Table 4. Analysis of Adverse Events**

| | | BioCell Collagen | related/outcome | placebo | related/outcome | *p* value |
|---|---|---|---|---|---|---|
| total no. in the group | | 35 | | 33 | | |
| total no. of adverse events | | 3 | | 6 | | 0.242 |
| total no. of subjects | | 3 (8.6%) | | 3 (9.1%) | | 0.940 |
| severity | | | | | | |
| mild | skin rashes | 1 | probable/recovered | | | |
| | vomiting | | | 2 | not related/recovered | |
| | dizziness | | | 1 | not related/recovered | |
| | pain increase | | | 1 | possible/recovered | |
| | increase in VAS/WOMAC | | | 1 | possible/ongoing | |
| moderate | increase in VAS/WOMAC | 2 | not related/recovered | | | |
| | high blood pressure | | | 1 | not related/not recovered | |
| severe | | 0 | | 0 | | |

with a mean score of 6.56 for the BCC group and from ranging from 4.7 to 9 with a mean score of 6.49 for the placebo group (data not shown). The study reported by Benito-Ruiz and colleagues (2009) on the effect of hydrolyzed collagen on joint comfort used a primary end point of decreased pain as defined by a decline of ≥30 mm on the VAS score.[17] We applied the hypothetical criteria to analyze the efficacy of BCC further. In the BCC group, as much as 35% of the subjects had a substantial degree (>30 mm in VAS) of pain reduction. In contrast, only 2.5% of the subjects in the placebo group had similar degrees of pain reduction. These study outcomes strongly suggested that BCC was significantly effective in reducing pain and in improving activities of daily living of patients suffering from progressive OA. In addition, joint line tenderness, although not a predetermined primary end point, disappeared from 82% (29 of 35) of the subjects in the BCC group who completed the study, whereas 51% (17 of 33) of the subjects taking the placebo had a similar effect (data not shown).

Comparisons between the BCC and the placebo groups on days 35 and 70 showed that there was a significant placebo effect on the study outcome. The placebo effect is well-documented in clinical trials conducted to assess changes in subjective osteoarthritic symptoms. However, significant improvements of WOMAC score from baseline in the placebo group did not negate the efficacy of BCC in reducing OA-associated symptoms because the improvement in the BCC group was significantly higher than that in the placebo group. Meanwhile, the analysis of WOMAC subscores showed that daily ingestion of BCC decreased the difficulties of various physical activities more effectively than stiffness, which contributed to significance in the improvement of WOMAC score on both days 35 and 70. Decrease in physical disabilities was considered to be associated with reduction of pain as measured by both VAS and WOMAC, although the WOMAC subscore of pain was lagging.

Potential mechanisms for the efficacy of BCC in managing osteoarthritic symptoms include processes directed at the synovium (and synovial fluid) and, second, at joint cartilage. First, the degradation of the synovium and synovial fluid during the progression of OA is well-known.[20] The hydrolyzed collagen components of BCC include LMW (bioavailable) peptides. Studies have shown that oral ingestion of hydrolyzed collagen type I or type II led to appearance of various collagen-derived peptides including Pro-Hyp in human blood and that Pro-Hyp peptide stimulated HA biosynthesis from synovium cells in vitro.[15,21] Therefore, ingestion of BCC containing hydrolyzed collagen type II may support improved or increased synovial fluid, helping to relieve pain and restricted joint movement. Second, BCC may facilitate the regeneration of cartilage. In a murine model, hydrolyzed collagen of average MW of 3.3 kDa was effectively absorbed into the small intestine and accumulated in the cartilage.[14] More interestingly, the chondrocytes, which are responsible for the synthesis and maintenance of the cartilage matrix, were stimulated in vitro by hydrolyzed collagen derived either from gelatin (hydrolyzed collagen type I) or from chicken sternal cartilage extract (hydrolyzed collagen type II) to produce collagen type II.[12] In contrast, undenatured (unhydrolyzed) collagen fails to stimulate chondrocytes. These results would support the hypothesis that BCC may act to modify the biochemical pathways that underlie osteoarthritic pathogenesis. Further studies employing radiological examination of the joint are warranted to investigate the effect of BCC on the course of joint degeneration due to OA.

BCC is not an artificial combination, but a naturally occurring matrix containing hydrolyzed collagen type II and LMW GAGs characterized by a specific composition and molecular weight range (1.5−2.5 kDa). It is postulated that the coexistence of LMW GAGs and hydrolyzed collagen type II generates a synergistic effect, which is crucial for the biological properties and efficacy of BCC.

This study provides the first clinical controlled study providing evidence that daily supplementation with BCC may deliver significant clinical benefits to OA patients with pain and disability. Further studies are needed to elucidate how this dietary supplement delivers its clinical benefits, especially in terms of potentially regenerating cartilage. Determining which subpopulation of OA patients, at what dose, is more likely to benefit from BCC remains unanswered.

In conclusion, BioCell Collagen was well-tolerated and provided significant symptom reduction in patients suffering from osteoarthritic pain and disability. Compared to placebo, it led to a significant pain reduction in knee and/or hip joint as measured by VAS pain assessment and to a significant improvement in their WOMAC scores. Although this trial, using a matrix of hydrolyzed collagen type II and LMW HA and chondroitin sulfate, improved OA-associated symptoms, in vitro and in vivo studies suggest that the mechanism of action may be through modification of underlying disease processes. BioCell Collagen may be considered as a safe and efficacious complement to current medical and dietary options in the management of OA symptoms.

## AUTHOR INFORMATION


### Corresponding Author

*Phone: +1 (714) 632-1231. Fax: +1 (714) 632-5866. E-mail: joosang@biocelltechnology.com.



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### Notes

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The authors declare the following competing financial interest(s): Joosang Park is a salaried employee of BioCell Technology, LLC at the time of submission. The other co-authors do not have any conflict of interest to declare.

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## ABBREVIATIONS USED

BCC, BioCell Collagen; GAGs, glycosaminoglycans; HA, hyaluronic acid; ICH, International Conference on Harmonization; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; Pro-Hyp, proline-hydroxyproline dipeptide; PGs, proteoglycans; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

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