

# An Osteoinductive Protein Complex That Stimulates Regeneration of Bone and Cartilage for Treatment of Moderate to Severe Osteoarthritis

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## Abstract

**Context:** Osteoarthritis, also known as degenerative joint disease, is one of the most common forms of joint disorder in the United States and affects over 20 million people. Current treatments for its management involve the use of analgesics such as acetaminophen and nonsteroidal, anti-inflammatory drugs (NSAIDs). These treatments, however, have shown limited effectiveness, and in some cases, have produced severe side effects, including GI conditions, internal bleeding, and kidney damage.

**Objective:** The study intended to demonstrate the clinical effects of a novel protein complex, Cyplexinol, in combination with glucosamine and chondroitin, in the regenerative stimulation of bone and cartilage to reduce pain and increase joint flexibility in healthy individuals with degenerative joint disease due to osteoarthritis.

**Design:** The research team conducted an open-labeled, randomized, prospective, multicenter trial.

**Setting:** The offices of the four licensed health-care professionals were the four centers in which the trial took place.

**Participants:** Participants were patients at the four health-care centers—18 women and 10 men with a mean age of 61 years.

**Intervention(s):** In this trial, the 28 randomized participants in the intervention group received a combination

of Cyplexinol, a bone morphogenetic protein (BMP) complex, plus glucosamine and chondroitin, three times a day. The total daily dose was 150 mg of Cyplexinol, 1500 mg of glucosamine sulfate, and 1200 mg of chondroitin sulfate for a period of 4 weeks.

**Outcome Measure(s):** The research team evaluated pain and joint flexibility using a visual analog scale (VAS). Participants completed the questionnaire at baseline and weekly thereafter to allow the research team to assess the effectiveness of the product.

**Results:** Based on the comparison of mean values reported at baseline, the research team noted a significant reduction at the end of the trial in overall pain (54.7%) as well as frequency of pain (58.8%) in the affected joints. Similarly, a significant reduction in pain and stiffness was reported during recreation/activity as participants moved the affected joints. This reduction in pain translated into an increase in the strength of the affected joints and an increase in overall activity for participants.

**Conclusions:** The results of this trial suggest that the combination of Cyplexinol, which contains BMPs and growth factors, plus glucosamine and chondroitin, reduced joint pain and stiffness effectively in individuals with reduced joint function associated with osteoarthritis.

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Osteoarthritis, also known as degenerative joint disease, is one of the most common forms of joint disorder in the United States and affects over 20 million people.<sup>1-3</sup> It is caused by the progressive breakdown and eventual loss of cartilage in the joints, affecting mostly the hands, feet, spine, hips, and knees. Available therapies for osteoarthritis primarily address the treatment of the patients' joint pain.<sup>4</sup> Current treatments for the management of osteoarthritis involve the use of analgesics such as acetaminophen and nonsteroidal, anti-inflammatory drugs (NSAIDs). These treatments, however, have shown limited effectiveness, and in some cases, have produced severe side effects, including GI conditions,

internal bleeding, and kidney damage.<sup>5-7</sup>

In addition to NSAIDs, the dietary supplements glucosamine and chondroitin sulfate, alone or in combination, have been commonly used in treatment of the symptoms of osteoarthritis and have been advocated as safe, but they have shown mixed results for the disease's management. Both of these nutrients are naturally found in and around the cells of cartilage. Glucosamine is an amino sugar that is produced in the body and is distributed in cartilage and other connective tissue. Chondroitin sulfate is a complex carbohydrate that helps cartilage to retain water.

In several clinical trials, the effectiveness of glucosamine and chondroitin sulfate has been investigated. Among these studies, two major, human clinical trials have investigated the role of these two dietary supplements. The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), a 1583-patient, 6-month trial sponsored by the National Institutes of Health,<sup>8</sup> failed to show significant improvement in the overall patient population for glucosamine, chondroitin, or their combination. The results of another trial with 318 participants treated for 6 months—the Glucosamine Unum In Die (once-a-day) Efficacy (GUIDE)—showed a small 5% to 6% improvement over placebo for glucosamine sulfate in the scores on the total Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index.<sup>9</sup> Because of the limited effectiveness of these treatments, the search for alternative and complementary treatments for osteoarthritis continues.

Conventional therapies have been designed to minimize the effects of the inflammatory response, which exacerbates the overall pathology, and have had minimal effects on the syndrome's etiology. In recent years, investigators have attempted to isolate and study the effect of proteins that stimulate regeneration of bone and cartilage by activating mesenchymal stem cells (MSC) and differentiating them into osteoblasts and chondrocytes that in turn promote bone-and-cartilage formation *de novo*.<sup>10-12</sup> Bone Morphogenetic Proteins (BMPs) have been shown to be the key osteoinductive proteins responsible for activating MSC, supported with key growth factors (TGF- $\beta$ , IGF, and bFGF) for cellular maturation. These osteoinductive proteins exhibit capabilities for joint-tissue repair as well as intrinsic anti-inflammatory properties, both of which are essential for repairing tissue damage in arthritic patients.<sup>13-15</sup> In a recent effort to develop a more effective supplement for individuals with joint pain, a unique complex of osteoinductive proteins, known as Cyplexinol, has been discovered. The research team combined this protein complex with glucosamine and chondroitin and investigated the combination to determine its effectiveness in reducing pain and increasing joint flexibility in individuals with degenerative joint disease due to osteoarthritic conditions.

## Methods

### Participants

The four licensed health-care professionals, who were members of the research team for the present study and are four of the authors of this article, provided the four centers for the multicenter trial at their respective offices. To be eligible, patients must have been 18 years of age or older and must have been diagnosed with a moderate-to-severe osteoarthritic condition in the hip or knee by a health-care professional. Patients were excluded from the trial if they were taking glucosamine/chondroitin/MSM/SAMe, omega-3, or any herbal product or other supplement for pain or inflammation of the joints. They were also excluded if they were taking any NSAIDs, COX-2 inhibitors, DMARDs, steroids/corticosteroids, TNF blockers, narcotics, or any controlled substances for pain as prescribed by a physician. Other exclusion criteria included (1) being a pregnant or nursing woman, (2) having diabetes, (3) being allergic to shellfish, and (4) having rheumatoid or another form of arthritis. The study also excluded individuals who could not or were unwilling to interrupt the intake of a medication or supplement for joint health for at least 1 month prior to beginning the trial.

Twenty-eight randomized patients—18 women and 10 men with a mean age of 61 years—were enrolled. To maintain anonymity, participants were alphabetized and then randomly assigned a number by selecting odd and even numbers from a random number table.

Prior to the start of the trial, participants were required to have a physical exam and a medical-history exam by one of the four licensed health-care professionals managing the study as well as to complete an initial visual analog scale (VAS) questionnaire to establish a baseline.<sup>16</sup> In addition to the physical and medical-history exam, an x-ray of the knee or hip joint was completed, at the discretion of the health-care professional, to further support the diagnosis.

### Intervention

The trial was conducted as an open-labeled, randomized, prospective, multicenter study. The test supplement used in this trial was a combination of Cyplexinol, which consists of Bone Morphogenetic Proteins (BMPs) that stimulate the regeneration of bone and cartilage, plus glucosamine and chondroitin. BMPs belong to the TGF-beta superfamily, which includes the following growth factors that also are present in the supplement: (1) transforming growth factor beta (TGF- $\beta$ ), (2) insulin-like growth factor (IGF), (3) basic fibroblast growth factor (bFGF), and (4) vascular endothelial growth factor (VEGF).

Treatment consisted of oral doses of Cyplexinol plus glucosamine and chondroitin in a combined tablet, taken three times a day for one month. The total daily dosage provided 150 mg of Cyplexinol, 1500 mg of glucosamine

sulfate, and 1200 mg of chondroitin sulfate.

The participants were evaluated for the tolerability of the intervention and for any adverse reactions associated with the supplement containing Cyplexinol plus glucosamine and chondroitin. If a patient withdrew from the trial, an exit questionnaire was conducted to understand the reason or cause. No additional participants were added as replacements.

## Outcome Measures

### VAS Questionnaire

To assess the effectiveness of the unique supplement, participants were required to complete the visual analog scale (VAS) questionnaire weekly. The questionnaire consisted of participants' indicating how they felt regarding their weekly pain by marking a line on the scale (arbitrarily from 0-4). The raw data was then transformed using a scalar function transform of  $y=y[x]K$  ( $K=2.5$ ) to allow the data to be expressed as a 10-point scale. Within the transition of the data, there was no significant shift in values. Table 1 shows the transformed scales on the questionnaire.

Data gathered from the VAS questionnaires were subjected to statistical analysis using a *t* test with Graphpad PRISM statistical analysis software (GraphPad Software, Inc, La Jolla, CA). One-way ANOVA was performed using GraphPad Prism software with a conservative post-hoc,

Dunnett's Multiple Comparison Test for each week and between weeks. The results were evaluated against the corresponding initial values and the significant change for each week was reported. With the means that were obtained from the statistical assessment of weeks 0, 1, 2, 3, and 4 the percent change and percent difference were calculated using the following formats: Percent change =  $(\text{Initial score} - \text{Week X}/\text{Initial}) \times 100$ ; Percent Difference =  $\text{Initial score} - \text{Week X}/\text{Average} (\text{Initial,Week X}) \times 100$

## Results

Of the 28 randomized participants that were enrolled, 23 participants completed the trial. The five participants who did not complete the trial dropped out due to lack of compliance; they did not follow up with their health-care professional during the 4-week trial.

For the 23 remaining participants, compliance with the trial's treatment regimen was excellent. For all participants who completed the trial, 100% submitted a VAS questionnaire weekly to their health-care professionals. No adverse effects of the treatment were reported by the participants.

Following treatment with Cyplexinol plus glucosamine and chondroitin, participants' scores for overall reduction in pain and frequency of pain from their weekly VAS questionnaires showed a rapid response to the treatment. This response occurred as quickly as 7 days after the supplementation commenced (Table 2). As the treatment continued, the overall pain and the frequency of pain of the affected joint continued to decrease. By the end of weeks 1, 2, 3, and 4, the overall reduction in pain from baseline was 26.5%, 37.7%, 46.7% and 54.7%, respectively. Similarly the frequency of pain was reduced by 21.9%, 36.2%, 48.7%, and 58.8%, respectively. The weekly evaluation of both pain and frequency of pain revealed a statistically significant improvement in both of these parameters.

By the end of the trial, the results of the statistical analysis indicated that treatment with a combination of Cyplexinol plus glucosamine and chondroitin significantly reduced overall pain ( $P < .0001$ ) by 54.7% of the affected joint (Figure 1). A significant reduction ( $P < .0001$ ) in the frequency of pain (58.8%) also occurred (Figure 2).

In addition, an increase in recreation/activity of 41.6% was reported at the end of week 4 of treatment that was the result of the decrease in pain. The increase in recreation/activity began during week 1 and was still improving at week 4 (Figure 3). Compared to the baseline value, strength also increased in the participants by 33% at the end of week 4 (Figure 4).

## Discussion

Osteoarthritis is the most common form of arthritis in the United States, affecting nearly 27 million Americans.<sup>17</sup> This debilitating disease also results in significant financial burden on the health-care system and society, costing the US economy nearly \$128 billion per year in medical

**Table 1.** VAS Questionnaire Scales (Transformed)

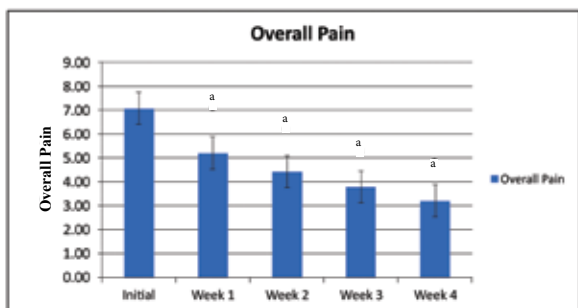
Category	Scale
Overall pain of the affected joint	0 = No pain
	2 = Mild pain (25% of the day)
	4 = Moderate pain (50% of the day)
	8 = Severe pain (75% of the day)
	10 = Worst possible pain (100% of the day)
Reduction in the frequency of pain	0 = No pain
	2 = Mild pain (25% of the day)
	4 = Moderate pain (50% of the day)
	8 = Severe pain (75% of the day)
	10 = Worst possible pain (100% of the day)
Reduction of pain during activity (activity level)	0 = Cannot do any activities
	2 = Can do a few activities
	4 = Can do some activities
	8 = Can do most activities
	10 = Can do all activities
Reduction in pain while lifting (strength)	0 = Increased pain with any lifting
	2 = Increased pain with light weight
	4 = Increased pain with moderate weight
	8 = Increased pain with heavy weight
	10 = No pain with heavy lifting

**Table 2.** Mean VAS Scores by Category in Cyplexinol Plus Glucosamine and Chondroitin Supplemented Group

	Overall Pain (Means±SEM)	Frequency of Pain (Means±SEM)	Recreation Activity (Means±SEM)	Strength (Means±SEM)
<b>Initial</b>	7.07±0.32	7.53±0.36	3.07±0.40	3.91±0.54
<b>Week 1</b>	5.20±0.34 <sup>a</sup>	5.88±0.45 <sup>a</sup>	4.68±0.59	4.67±0.55
<b>Week 2</b>	4.41±0.47 <sup>a</sup>	4.81±0.53 <sup>a</sup>	5.35±0.62 <sup>a</sup>	4.93±0.59
<b>Week 3</b>	3.77±0.40 <sup>a</sup>	3.87±0.59 <sup>a</sup>	6.10±0.47 <sup>a</sup>	5.74±0.47
<b>Week 4</b>	3.20±0.41 <sup>a</sup>	3.10±0.47 <sup>a</sup>	7.01±0.48 <sup>a</sup>	5.43±0.55 <sup>a</sup>

<sup>a</sup>Indicates values are significantly different from baseline at  $P < .05$ .

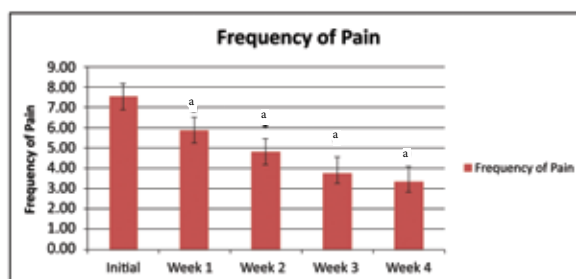
**Figure 1.** Effect of Cyplexinol Plus Glucosamine and Chondroitin on Overall Pain, Measured Weekly



The figure shows results for 4 weeks for affected joints in participants with osteoarthritis.

Note: The values are presented as means ± standard error.  
<sup>a</sup>Represents values significantly different from control at  $P < .05$ .

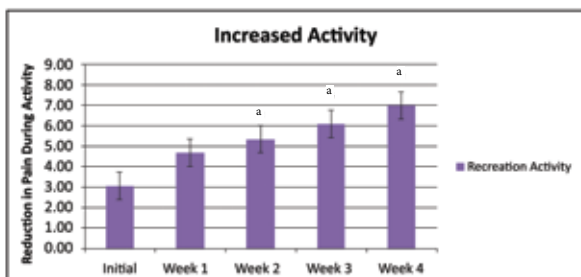
**Figure 2.** Effect of Cyplexinol Plus Glucosamine and Chondroitin on Reduction in Frequency of Pain, Measured Weekly



The figure shows results for 4 weeks for affected joints in participants with osteoarthritis.

Note: The values are presented as means ± standard error.  
<sup>a</sup>Represents values significantly different from control at  $P < .05$ .

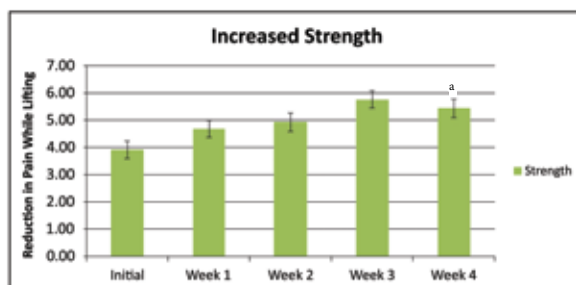
**Figure 3.** Effect of Cyplexinol Plus Glucosamine and Chondroitin on Increase in Activity Levels, as Measured by a Reduction in Pain During Recreation/Activity



The figure shows results for 4 weeks for affected joints in participants with osteoarthritis.

Note: The values are presented as means ± standard error.  
<sup>a</sup>Represents values significantly different from control at  $P < .05$ .

**Figure 4.** Effect of Cyplexinol Plus Glucosamine and Chondroitin on Increase of Strength, as Measured by a Reduction in Pain During Lifting



The figure shows results for 4 weeks for affected joints in participants with osteoarthritis.

Note: The values are presented as means ± standard error.  
<sup>a</sup>Represents values significantly different from control at  $P < .05$ .

care and indirect expenses, including lost wages and productivity.<sup>18</sup> The present trial was designed to evaluate the efficacy and safety of a unique combination of Cyplexinol, a protein complex stimulating bone and cartilage regeneration that contains BMPs, plus glucosamine and chondroitin, as a treatment option for osteoarthritis.

The results of the present preliminary trial support the effectiveness of Cyplexinol plus glucosamine and chondroitin for the symptomatic treatment of moderate to severe osteoarthritis. The results also indicate that the combined formulation relieves pain quickly as reported by participants, with a reduction of pain in one week. The combination of Cyplexinol plus glucosamine and chondroitin has the added benefit of avoiding the side effects associated with long-term use of other osteoarthritis treatments such as NSAIDs.<sup>5-7</sup>

In the present trial, participants experienced a relatively rapid response in the overall pain and the frequency of pain as evaluated by a visual analog scale (VAS) questionnaire, with a mean decrease of 26.5% for overall pain and 21.9% for frequency of pain after one week. By the end of the trial period (28 days), the mean response was approximately 54.7% for overall pain and 48.6% for frequency of pain. These observations are superior to the responses shown for glucosamine and chondroitin in previous clinical investigations.<sup>8,9</sup> The measures of subjective symptoms of osteoarthritis, such as pain and stiffness, and the wide variation in individual patient's perceptions of these symptoms, result in complex relationships that can be difficult to elucidate from the reporting of mean treatment effects in clinical trials. These measures may fail to adequately describe the potential benefits to the individual patient.<sup>19-22</sup> In the present trial, VAS was used. Visual analog and categorical scales have been reported to be effective in determining average pain due to osteoarthritis.<sup>23</sup>

Compared to the conventional treatment with products such as glucosamine and chondroitin, the results of this trial also suggest that an additional mechanism of action may be at work. The rapid onset of action and the high percentage of participants with clinical improvement from administration of Cyplexinol plus glucosamine and chondroitin, may indicate an anti-inflammatory process due to the Cyplexinol protein complex. The BMPs within Cyplexinol have been well documented within the medical and scientific literature to exhibit not only bone and cartilage regenerative properties but anti-inflammatory properties as well.<sup>24</sup> The regeneration of tissue could also influence the degree of pain by reversing the degenerative process.

The onset of healing and diminution of inflammatory processes also appear to affect the increase of proinflammatory cytokines within the affected tissues. These cytokines have been linked to the destruction of cartilage in osteoarthritis by activating the Interleukin-1 (IL-1) pathway and its downstream components.<sup>15,25</sup> Excessive levels

of IL-1 in the synovial tissue have been associated with greater attrition of bone and cartilage. IL-1 is a proinflammatory cytokine that binds to the IL-1 receptor type 1, leading to the activation of the NF-kb transcription factor and expression of matrix metalloproteinase.<sup>14</sup>

To restore the joint damage due to osteoarthritis, strategies exploring the consequences of blocking or stopping the targets of these cytokines are required. In this regard, the results of this present trial following treatment with Cyplexinol, which contains BMPs, plus glucosamine and chondroitin, have shown promise as a natural alternative. The regeneration of cartilage and bone tissue may, therefore, have a direct effect on inflammation through interaction with inflammatory cytokines.

The progression of osteoarthritis has been shown to depend on the degradation of type II collagen and proteoglycan molecules.<sup>26,27</sup> Interstitial collagenases, such as matrix metalloproteinase or MMP-1, MMP-8, and MMP-13 that are upregulated by IL-1, are reported to degrade type II collagen in cartilage. Among these collagenases, elevated levels of MMP-1 and MMP-13 have been observed in arthritic tissues.

The TGF- $\beta$  superfamily of proteins, such as BMP-2 and TGF- $\beta$ , has an immunosuppressive effect against the IL-1 pathway and a protective effect against collagen degradation by inhibiting MMP-1 and MMP-13 expression.<sup>25,28,29</sup> In vivo studies have shown that BMP-2 and TGF-beta induce proteoglycan synthesis.<sup>30,31</sup> The mechanism of action of the constituents of the unique complex used in the present trial, and particularly that of Cyplexinol, such as BMP-2 and TGF-b, appears to be related to the induction of synthesis of proteoglycan molecules, resulting in the arrest of the progression of osteoarthritis as well as recovery.

In spite of the present preliminary trial's limitations, such as the fact that it was open-labeled, had a small sample size, and used VAS, its results suggest that oral administration to subjects suffering from osteoarthritis of an osteoinductive protein complex, Cyplexinol, plus glucosamine and chondroitin, reduces overall pain and frequency of pain. The results of the present trial, in conjunction with previously published data, indicate a new paradigm in scientists' understanding of the pathogenesis of osteoarthritis and suggest a relationship between exogenous BMP-signalling via oral administration and joint function and repair. As such, the BMPs in Cyplexinol may provide important new tools in the clinical management of moderate to severe osteoarthritis. In conclusion, treatment with a combination of Cyplexinol plus glucosamine and chondroitin was found to be effective for people with moderate to severe, joint pain and stiffness.

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