The Effects of Milk Protein Concentrate on the Symptoms of Osteoarthritis in Adults: An Exploratory, Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

**Background:** Reconstituted hyperimmune milk product has been shown to have anti-inflammatory qualities, prompting further research into its use for the relief of osteoarthritis symptoms. A concentrated form of this milk product, milk protein concentrate (MPC), contains the high-molecular-weight and low-molecular-weight components present in the reconstituted milk product.

**Objective:** The purpose of this exploratory study was to assess the effects of MPC on the symptoms of osteoarthritis in adults.

**Methods:** Patients aged ≥ 19 years with physician-diagnosed osteoarthritis with daily joint pain, stiffness, and immobility were eligible. This was a prospective, randomized, double-blind, placebo-controlled trial lasting 6 weeks and having 3 treatment arms: MPC 2000 mg BID, glucosamine sulfate 500 mg TID, and placebo. Osteoarthritis symptoms were assessed using the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index.

**Results:** Forty-two participants were enrolled (8 men, 34 women; mean age, 59 years [range, 34-86 years]); 35 patients (5 men, 30 women) completed the study. Due to significant baseline differences in 3 (stiffness, activities, and total) of the 4 (pain, stiffness, activities, and total) WOMAC Osteoarthritis Index scores in the placebo group compared with the MPC- and glucosamine sulfate-treated groups ($P \leq 0.05$), the results of this study were restricted to the analysis of intragroup performance from baseline to the completion of the study. The results showed significant improvement from baseline to week 6 for the MPC-treated group for all 4 scores ($P \leq 0.005$). In the glucosamine sulfate-treated group, a significant improvement was found in stiffness and total WOMAC Osteoarthritis Index scores from baseline to week 6 ($P \leq 0.05$ for both) but not in the pain or activities scores. In the placebo group,
no significant changes were found in any of the WOMAC Osteoarthritis Index scores.

**Conclusion:** The results of this study indicate that MPC, when given at a dose of 2000 mg BID, was effective in relieving the symptoms of osteoarthritis, including joint pain, joint stiffness, and immobility, in this patient population.

**Key words:** osteoarthritis, milk protein concentrate, glucosamine sulfate, hyperimmune milk, Western Ontario and McMaster Universities Osteoarthritis Index, neutrophil. *(Curr Ther Res Clin Exp. 2002;63:430-442)*

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**INTRODUCTION**

The beneficial effects of milk and other dairy products on health have been recognized for centuries. In 1892, Ehrlich published his observation that mothers transfer disease immunity to their offspring through breastfeeding. In 1908, Metchnikoff attributed the beneficial effects of yogurt to the metabolic products of bacterial fermentation. In 1955, Petersen and Campbell presented evidence that cow's milk immunized with a polyvalent vaccine made from human pathogenic bacteria contained high levels of antigen-specific antibodies.

Since 1958, research has been conducted on the health benefits of hyperimmune milk from cows exposed to a specific proprietary immune stimulant. The hyperimmune milk is derived from a process that involves the delivery of an immune stimulant to pregnant cows, beginning 4 weeks before parturition and continuing every 2 weeks throughout lactation. The milk from these specially treated cows is collected and processed according to routine dairy product-handling procedures and undergoes a proprietary pasteurization process that preserves the biologically active ingredients. The details of the proprietary immune stimulant, the procedure for the immunization of cows, and the procedure for processing the milk have been previously published. This research eventually led to the confirmation that this process resulted in the increased expression of naturally occurring, biologically active factors in the milk. In addition to high-molecular-weight (HMW) immunoglobulins (Ig) (antigen-specific IgG antibodies), the milk also was discovered to have low-molecular-weight (LMW) components with anti-inflammatory activity.

When given as hyperimmune milk reconstituted from dry milk powder, the addition of the milk to the diet of volunteers was found to considerably relieve the painful symptoms of both rheumatoid arthritis and osteoarthritis. Beck reported on a 12-month, randomized, double-blind, placebo-controlled, crossover study by Niedermeier in 20 patients with rheumatoid arthritis. The study compared the effects of a commercially available, conventional skim milk powder with placebo using a 6-component questionnaire. The results revealed a significant improvement in joint pain, stiffness, and swelling in the treatment group compared with the control group (P ≤ 0.015).
The effectiveness of the hyperimmune milk powder in patients with osteoarthritis was initially documented in a large, open-label survey conducted from 1961 to 1989 by Stolle Milk Biologics, Inc (SMBI). In this survey, called the Ohio Survey, >8000 patients with osteoarthritis were given 45 g of the hyperimmune milk powder to reconstitute and drink daily. From 1992 to 1996, patients with osteoarthritis were asked to record and rate their joint symptoms quarterly using a questionnaire. The results of this survey revealed that 1092 of 1362 (80.2%) respondents reported considerable improvement in joint pain with reconstituted hyperimmune milk product. In addition, 896 of 1245 (72.0%) respondents reported considerable improvement in morning stiffness. The results of the Ohio Survey, together with the other available research describing the anti-inflammatory qualities of this specialized milk powder, prompted further research into the use of this milk product for the relief of osteoarthritis symptoms.

The reconstituted hyperimmune milk product used in the Niedermeier study reported on by Beck and the Ohio Survey, although effective and well tolerated, was inconvenient to take and time consuming to prepare. A more efficient formulation was needed. Therefore, a concentrated form of the milk product, milk protein concentrate (MPC), was developed by SMBI in 1999 and contains both the HMW and LMW components present in the reconstituted milk product. The concentration process for the MPC removed 95% of the lactose and salt, thereby reducing the mass sufficiently to allow it to be produced in capsule form. To confirm the presence of HMW components, the MPC was tested using enzyme-linked immunosorbent assay and found to contain 9.456 mg IgG per gram and a specific antibody titer of 1:20,484. To confirm the presence of LMW components, an indirect assay for anti-inflammatory activity was used because direct measurement of these components was not yet possible. The protein-free organic extracts of the MPC were tested topically using the standard 12-0-tetradecanoylphorbol-13-acetate mouse ear swelling model and was found to have a significant anti-inflammatory effect ($P \leq 0.05$). The MPC used in this trial was subjected to these same assays and was found to contain both the HMW and LMW components at levels well within the acceptable limits set for the reconstituted hyperimmune milk product.

The purpose of this study was to assess the effects of MPC on the symptoms of osteoarthritis. A randomized, double-blind protocol was designed to assess the effectiveness of MPC, compared with glucosamine sulfate and placebo, on the symptoms of pain, stiffness, and immobility in a population of patients with osteoarthritis. Glucosamine sulfate was selected for comparison because of its recent attention as a symptom-modifying and possibly structure-modifying dietary supplement for osteoarthritis.

**PATIENTS AND METHODS**

**Patients**

This was a single-center study conducted at the Minnesota Applied Research Center. Outpatients aged ≥ 19 years with physician-diagnosed osteoarthritis
and daily joint pain, stiffness, and immobility were eligible for the study. Excluded were
patients who required continued prescription medication for arthritis, were
nonambulatory due to arthritis, had an active major organ system disease, or were
pregnant or lactating. This study was approved by the Western Institutional Review
Board (Olympia, Wash). All participants gave written informed consent to participate.

Study Design
This was a prospective, randomized, double-blind, placebo-controlled trial lasting 6
weeks. Patients were randomized to receive MPC* 2000 mg BID, glucosamine sulfate
500 mg TID, or placebo (rice powder). So that the placebo would be applicable to both
of the other treatment arms, rice powder, rather than skim-milk powder, was chosen as
the placebo. The glucosamine sulfate dose was chosen after a review of previous studies
having a moderate to large treatment effect using oral glucosamine sulfate versus
placebo in patients with osteoarthritis. All ingredients were manufactured in
indistinguishable capsules. Additional placebo capsules were used to assemble study
capsule packets, such that each patient received 4 capsules TID, containing either active
ingredient or placebo according to his or her treatment arm. Study-capsule packets were
precoded by the manufacturer according to a randomization table and labeled for
morning, noon, and evening dosing to maintain the proper sequence of dosing in each
treatment arm. Investigators were blinded to the randomization code. Adverse events
and medication compliance were assessed at biweekly clinic visits by the study
investigator(s). In the event of intractable joint symptoms, patients were advised by the
study investigator(s) to use approved rescue medications, including naproxen 220 mg,
ibuprofen 200 mg, acetaminophen 325 mg, and acetylsalicylic acid 325 mg. Each dose
of these individual medications was given a score of 1 point, and the use and amount of
rescue medications were recorded by the study investigator(s) at biweekly visits.

Measurements
Joint symptoms were assessed using the Western Ontario and McMaster Universities
(WOMAC) Osteoarthritis Index, a validated questionnaire. The WOMAC Osteoarthritis Index includes scores for pain, stiffness, and activities, as well as a total score. The WOMAC Osteoarthritis Index Scores were transformed according to the
standard orthopedic formula.

\[
\text{Transformed scale} = 100 - \frac{\text{Actual raw score} \times 100}{\text{Possible raw source}}
\]

The values represent "percentage of normal," such that increasing scores reflect
improvement and decreasing scores reflect worsening of symptoms. The

*Trademark: Microlactin™ (Stolle Milk Biologics, fne, Cincinnat, Ohio).
WOMAC Osteoarthritis Index was completed by patients at baseline and again at weeks 2, 4, and 6. Vital signs (blood pressure, heart rate, and temperature) and body weight were measured by the study investigator(s) at baseline and, again at weeks 2, 4, and 6 using digital assessment equipment. Blood samples for the determination of a complete blood count and chemistry profile were obtained using venipuncture at baseline and week 6 and were analyzed by Quest Diagnostics, Minneapolis, Minnesota.

**Statistical Analysis**

Testing by an independent statistician for normality of variable distributions (Lilliefors test) revealed that the WOMAC Osteoarthritis Index variables were not normally distributed. Therefore, nonparametric methods were used by the statistician to compare the groups. Baseline characteristics were compared between treatment groups using 1-way nonparametric analyses of variance (Kruskal-Wallis test). To assess changes over time within each group, the computed change from baseline was compared for all measured variables at weeks 2, 4, and 6 using Mann-Whitney tests. Statistical significance was defined as $P \leq 0.05$. Cases were excluded on an analysis-by-analysis basis for missing values.

**RESULTS**

**Study Population**

Forty-two participants were enrolled (8 men, 34 women; mean age, 59 years [range, 34-86 years]). Of the 42 patients randomized, 35 (5 men, 30 women) completed the study-12 in the MPC-treated group, 13 in the glucosamine sulfate—treated group, and 10 in the placebo group. Of the patients who did not complete the study, 2 patients in the MPC-treated group were withdrawn. One of these patients was withdrawn due to gastritis, which occurred on day 40 after receiving naproxen 220 mg, 1 tablet BID for 4 weeks, as a rescue medication for persistent arthritis symptoms. Endoscopic evaluation revealed gastritis and small punctate ulcerations consistent with the effects of nonsteroidal anti-inflammatory drug (NSAID) use. Another patient In the MPC-treated group was withdrawn for lack of compliance with the study protocol. One patient in the glucosamine sulfate-treated group was withdrawn at week 2 after developing costochondritis, which required treatment with a non-protocol-approved NSAID. In the placebo group, 4 patients were withdrawn due to lack of compliance with the study protocol (1), dysphagia related to swallowing study capsules (1), and unhappiness with aspects of the study protocol (2). The baseline characteristics of participants who completed the study are listed in Table I. Analysis of baseline characteristics revealed significant between-group differences for the stiffness scores ($P = 0.004$), activities scores ($P = 0.05$), and total WOMAC Osteoarthritis Index scores ($P = 0.03$). Baseline WOMAC Osteoarthritis Index scores were significantly lower in the MPC-
Table I. Baseline demographic characteristics of patients who completed the study (N = 35).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glucosamine Sulfate</th>
<th>Placebo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60 ± 11</td>
<td>57 ± 13</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Female 9</td>
<td>11</td>
</tr>
<tr>
<td>Body Weight, kg</td>
<td>81 ± 19</td>
<td>73 ± 24</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>138 ± 18</td>
<td>134±20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82 ± 6</td>
<td>75 ± 11</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>81 ± 11</td>
<td>76 ± 11</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>36.7 ± 0.4</td>
<td>36.7 ± 0.4</td>
</tr>
</tbody>
</table>

WOMAC Osteoarthritis Index scores
- Pain                          62.9 ± 14.1          58.5 ± 8.8        76.0 ± 16.5
- Stiffness                     52.1 ± 16.7          40.4 ± 16.3       72.5 ± 9.9†
- Activities                   62.1 ± 12.6          59.8 ± 12.4       74.7 ± 14.4‡
- Total                         61.4 ± 12.6          57.8 ± 10.5       74.8 ± 13.7§

MPC = milk protein concentrate; WOMAC = Western Ontario and McMaster Universities.
*Mean ± SD (Kruskal-Wallis test).
†P = 0.004.
‡P = 0.05.
§P = 0.03.

glucosamine sulfate-treated groups than in the placebo group (P≤0.05), indicating more severe baseline symptoms in the 2 treatment groups. Considering the significant between-group differences at baseline, the groups could not be compared with each other. Therefore, the statistical analysis was limited to examining only the Intragroup performance from baseline to the completion of the study.

Survey Results
Table II lists the mean change from baseline for all 4 (pain, stiffness, activities, and total) WOMAC Osteoarthritis Index scores in each group at weeks 2, 4, and 6. In the MPC-treated group, significant Improvement occurred in all 4 WOMAC Osteoarthritis Index scores at weeks 2, 4, and 6 (see Table II for P values).

In the glucosamine sulfate-treated group, significant improvement occurred in pain and stiffness at week 2 (P = 0.05 and P = 0.01, respectively), and significant improvement occurred in all 4 WOMAC Osteoarthritis Index scores at week 4 (P = 0.04, P = 0.007, P = 0.03, and P = 0.03, respectively). For the glucosamine sulfate-treated group at week 6, significant changes occurred in the stiffness and total WOMAC Osteoarthritis Index scores (P = 0.01 and P = 0.05, respectively).
Table II. Western Ontario and McMaster Universities (WOMAC Osteoarthritis Index results (N = 35).

<table>
<thead>
<tr>
<th>WOMAC Osteoarthritis Index Score</th>
<th>Week</th>
<th>MPC* (P)</th>
<th>Glucosamine Sulfate* (P)</th>
<th>Placebo*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>2</td>
<td>10.5 ± 10.1 (0.005)</td>
<td>12.7 ± 23.9 (0.05)</td>
<td>-3.5 ± 7.1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>12.3 ± 14.2 (0.01)</td>
<td>16.5 ± 25.1 (0.04)</td>
<td>-1.0 ± 8.8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>19.6 ± 16.2 (0.003)</td>
<td>16.2 ± 25.8 (NS)</td>
<td>0.5 ± 15.0</td>
</tr>
<tr>
<td>Stiffness</td>
<td>2</td>
<td>14.8 ± 20.0 (0.03)</td>
<td>16.3 ± 18.0 (0.01)</td>
<td>-6.3 ± 13.5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>21.6 ± 17.8 (0.007)</td>
<td>17.3 ± 16.6 (0.007)</td>
<td>-3.8 ± 15.6</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>21.6 ± 14.9 (0.004)</td>
<td>19.2 ± 20.2 (0.01)</td>
<td>-2.5 ± 16.5</td>
</tr>
<tr>
<td>Activities</td>
<td>2</td>
<td>8.9 ± 12.9 (0.03)</td>
<td>10.7 ± 19.2 (NS)</td>
<td>-2.9 ± 8.6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>13.8 ± 12.1 (0.006)</td>
<td>12.8 ± 19.6 (0.03)</td>
<td>-2.6 ± 8.8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>18.0 ± 12.2 (0.004)</td>
<td>13.2 ± 23.5 (NS)</td>
<td>2.3 ± 12.0</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>9.8 ± 12.1 (0.02)</td>
<td>11.7 ± 19.4 (NS)</td>
<td>-3.3 ± 7.8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>14.1 ± 12.3 (0.005)</td>
<td>14.1 ± 19.9 (0.03)</td>
<td>-2.3 ± 8.1</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>18.7 ± 12.5 (0.005)</td>
<td>14.4 ± 23.3 (0.05)</td>
<td>1.5 ± 12.5</td>
</tr>
</tbody>
</table>

MPC = milk protein concentrate.
*Mean change from baseline ± SD (Mann-Whitney test)
†P=NS for all.

but no significant changes were found in the pain or activities scores. Throughout the study, no significant changes occurred in the WOMAC Osteoarthritis Index scores for the placebo group. The figure illustrates the mean change in normalized total WOMAC Osteoarthritis Index scores for each of the 3 treatment groups.

Other Measured Variables.

In the MPC-treated group, significant decreases occurred in heart rate (4.0 beats/mi at week 4 [P= 0.01] and 10.0 beats/min at "Week 6 [P= 0.03D. Also in the MPC-treated group, a significant increase of 88.78 cells/µL occurred in the serum absolute neutrophil count from baseline to week 6 (P = 0.03).

The use of rescue medications was monitored throughout the study for all 3 treatment arms (Table III). No significant changes were found within the groups regarding the use of rescue medications. One of the 6 patients in the MPC-treated group skewed the average by receiving 168 rescue medications in a 2-week period, a rate 2.8-fold higher than the next-highest rate. This same patient had taken no rescue medications at the 4- and 6-week periods. Lastly, no other significant changes were found within the groups for any of the other monitored variables.

Tolerability

All adverse events are listed in Table IV, whether or not they were thought to be related to treatment. In the MPC-treated group, of the 8 adverse events reported,
Figure 1, Normalized Total WOMAC Scores

![Normalized Total WOMAC Scores](image)

*Mean ± SEM

**Figure.** Normalized total Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index scores (mean ± SEM) of patients who completed the study (N = 35). MPC = milk protein concentrate.

3 were judged to be possibly related to the use of MPC. One patient reported excessive gas and bloating, and 1 patient reported both urinary frequency and dry mouth. In the glucosamine sulfate-treated group, 15 adverse events were reported, 2 of which were nausea after glucosamine sulfate cap-

**Table III.** Number of rescue medications used within each group for each 2-week period (N = 42; dropouts are included).

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Week 2* (Range)</th>
<th>Week 4* (Range)</th>
<th>Week 6* (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPC</td>
<td>22.9(9-36)</td>
<td>6.6(3-10)</td>
<td>5.8(3-9)</td>
</tr>
<tr>
<td></td>
<td>(n = 6)</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>Glucosamine Sulfate</td>
<td>5.3(3-8)</td>
<td>5.9(3-9)</td>
<td>9.9(4-15)</td>
</tr>
<tr>
<td></td>
<td>(n = 6)</td>
<td>(n = 5)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>Placebo</td>
<td>11.5(4-20)</td>
<td>14.4(6-23)</td>
<td>11.4(3-20)</td>
</tr>
<tr>
<td></td>
<td>(n = 4)</td>
<td>(n = 5)</td>
<td>(n = 4)</td>
</tr>
</tbody>
</table>

MPC = milk protein concentrate

*Mean ± SD (Mann-Whitney test). \( P = \text{NS} \) for all 3 groups at all 3 weeks
Table IV. Adverse events (N = 42; dropouts are included).

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>MPC (n = 14)</th>
<th>Glucosamine Sulfate (n = 14)</th>
<th>Placebo (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costochondritis</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Facial Edema, erythema</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Frequent bowel movement</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Excessive gas, bloating</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Gastritis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hives</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Malodorous Urine</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Muscle Cramps</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ruptured Ovarian Cyst</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sinus Symptoms</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Testicular Discomfort</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Frequency</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

MPC = milk protein concentrate

sules were received and judged to be possibly related to the use of glucosamine sulfate. No long-term adverse events of any treatment were reported.

DISCUSSION
Osteoarthritis, also called degenerative joint disease, is a slowly destructive process of the joint. In the United States, >16 million people are estimated to be afflicted with osteoarthritis, and, by the year 2020, >59 million people are estimated to be affected. 17 Although the exact biochemical cause of osteoarthritis remains unknown, the process usually begins with an abnormal joint structure or an unusually high stress placed on a joint surface over time.18,19 Much of the disease progression is due to mechanical stress on the joint, and, over time, the excessive stress can induce metabolic and structural changes in the cartilage, bone, and articular surfaces.19 The secondary inflammation due to progressive articular destruction appears to be focal and localized to the particular joint being affected. Symptoms of individuals with osteoarthritis include joint pain, stiffness, and immobility, which were measured in this study using the WOMAC Osteoarthritis Index.
Due to the side effects associated with current anti-inflammatory medical treatments,19 new and unique anti-inflammatory compounds that show effectiveness and favorable side-effect profiles should be considered as possible treatments for this currently incurable disease.

Exposing cows to a proprietary immune stimulant results in an increase in the synthesis and excretion, in the milk, of anti-inflammatory components that are normally present in cow's milk.20 The concentrated formulation of the hyperimmune milk powder derived from this process, MPC, was used in this study to test anti-inflammatory activity in adults with osteoarthritis.

The present study assessed changes in osteoarthritic symptoms with the use of MPC, glucosamine sulfate, and placebo, comparing results to initial baseline status. Patients receiving MPC scored significantly better in all 4 categories of the WOMAC Osteoarthritis Index at weeks 2, 4, and 6 than at baseline (see Table II for P values). Patients receiving glucosamine sulfate had significant improvement in some WOMAC Osteoarthritis Index scores at weeks 2, 4, and 6 compared with baseline (see Table II for P values). No significant improvement occurred in WOMAC Osteoarthritis Index scores in the placebo group.

We speculate that the decrease in heart rate in the MPC-treated group at weeks 4 and 6 may be a physiologic response secondary to the relief of acute and chronic pain in these individuals rather than a direct response to the compound itself. Further research is needed to investigate this response more fully.

The analysis of baseline characteristics between the 3 randomized groups revealed that the baseline WOMAC Osteoarthritis Index scores were significantly lower in the MPC- and glucosamine sulfate-treated groups than in the placebo group (P ≤0.05), indicating more severe baseline symptoms in the MPC- and glucosamine sulfate-treated groups. We suggest that future researchers stratify the randomization according to baseline WOMAC Osteoarthritis Index scores. A significant improvement in WOMAC Osteoarthritis Index Scores was seen in patients taking MPC (P ≤0.005). Although the MPC used in this research has both the HMW (antibody) component and LMW (anti-inflammatory) component, we believe the favorable improvement in symptoms in these individuals was due to the anti-Inflammatory component. Evidence for this conclusion is based on the fact that the inflammation seen with osteoarthritis is localized to the joint and is multifactorial but in part neutrophil mediated.21

Research by Ormrod and Miller,7 using the LMW anti-inflammatory component from hyperimmune milk, demonstrated suppression of inflammation and an increase in circulating neutrophil count in animal models. They speculated that this component might inhibit inflammation by interfering with the ability of neutrophils to emigrate from the vascular space, and they conducted in vivo studies that demonstrated that this compound suppressed neutrophil emigration by ≤75%. In a follow-up in vitro study, Stelwagen and Ormrod22 demonstrated the formation and maintenance of vascular tight junctions on exposure to the hyperimmune milk anti-inflammatory component,
theorizing that the anti-inflammatory properties of this compound may be mediated by restriction of the extravasation of neutrophils through vascular tight junctions. The present study demonstrated a significant increase in the circulating absolute neutrophil count in the MPC-treated group (P = 0.03).

Some useful parallels can be drawn between the activity of MPC and other anti-inflammatory agents. Glucocorticoids share anti-inflammatory properties linked to the inhibition of neutrophil functions. Multiple mechanisms are involved in the suppression of inflammation by glucocorticoids, including decreased release of vasoactive and chemoattractive factors, diminished secretion of proteolytic enzymes, and decreased emigration of neutrophils to areas of injury and inflammation. Miller et al have shown activity similar to that of glucocorticoids involving neutrophil activity and emigration with hyperimmune milk-derived anti-inflammatory compounds.

The results of the present study support the data from previous studies regarding the theory that MPC inhibits inflammation by decreasing the emigration of neutrophils and may do so by restricting extravasation of neutrophils through vascular tight junctions. Future research should include a design to investigate this possible mechanism of action more completely.

CONCLUSIONS
The results of this clinical study reveal that MPC 2000 mg BID was effective in relieving the symptoms of osteoarthritis, including joint pain, stiffness, and immobility as assessed using intragroup analysis from baseline to 6 weeks in this patient population. These results seem to indicate that the mechanism of action of MPC may involve the inhibition of neutrophil emigration from the vascular space to the site of osteoarthritic injury.

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