ABSTRACT

A questionnaire method was designed for dog owners to monitor the orthopedic disabilities of their pets for evaluation of a nutraceutical with joint health claims. Fifty large-breed dogs, 7 to 12 years of age, presenting with signs of osteoarthritis, were randomly allocated to placebo and active treatment groups. Degree of disability was assessed by physical examination, a standard questionnaire on daily activities, and a case-specific questionnaire that monitored specific impairments of each dog. The test product was a special milk protein concentrate (SMPC) from hyperimmunized cows, previously shown to express antiinflammatory and antiarthritic activity in humans. After a 1-week run-in period of dosing with placebo, each dog was randomly assigned to a treatment and given gelatin capsules containing either SMPC or a placebo twice daily for 8 weeks. Overall improvement was noted in 68% and 35% of the SMPC and placebo groups, respectively. Significant ($P < .05$) improvement in mean standardized and patient-specific questionnaire scores and in owner global assessments was detected in the SMPC group but not in the placebo group. Compared with the placebo group, the treatment response was significantly better in the SMPC group with regard to case-specific scores ($P < .001$) and owner global assessments ($P = .004$). The product was well tolerated and serum chemistry findings remained within normal limits.

INTRODUCTION

Objective assessment of clinical outcome is a continuing challenge in veterinary therapeutics. This is particularly true in conditions such as osteoarthritis\(^1\) for which there are few universally accepted biochemical markers\(^2,3\) or other objective measurements of severity or response to therapy. Force plate evaluations in horses\(^4\) and dogs\(^5,6\) provide objective clinical data but require resources unavailable to most veterinary practitioners. For drugs such as NSAIDs with known structure and biologic targets, pharmacokinetic/pharmacodynamic analyses are universally accepted approaches.\(^7,8\) However, nutraceuticals such as glucosamine and chondroitin products with poorly defined mechanisms of action cannot be readily evaluated by traditional approaches. For this reason, subjective questionnaires have been developed and validated in human patients with arthritis and utilized in clinical evaluation of nutraceuti-
In veterinary medicine, evaluation of nutraceuticals represents similar challenges. In humans, the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), which monitors the degree of difficulty performing daily activities, has become the standard for osteoarthritis trials. The sensitivity of standard questionnaires was increased in patients with rheumatoid arthritis by the McMaster-Toronto Arthritis (MACTAR) approach, which tracks the specific functions of concern to a particular patient. Although questionnaire-based outcome measures have been refined over the years, applied to conditions other than rheumatic diseases and are as effective as any available clinical measure, including laboratory tests and radiographs, to measure functional disability, they have not been as widely utilized in veterinary medicine.

A questionnaire-based method has been developed that combines both the WOMAC (standardized) and MACTAR (patient-specific) approaches for evaluation of musculoskeletal disabilities in dogs, and a clinical trial was designed to evaluate a dietary supplement with joint health claims. This supplement was a special milk protein concentrate (SMPC) prepared from the milk of hyperimmunized cows that has antiinflammatory activity and suppresses autoimmune disease in laboratory animals.

Milk contains a number of bioactive components, including immunoglobulins, cytokines, enzymes, hormones, and growth factors. The recognition of antiinflammatory properties of human breast milk and milk from hyperimmunized cows suggests that dairy ingredients may also be of therapeutic value in orthopedic conditions. SMPC has no demonstrable cyclooxygenase- or lipoxygenase-inhibiting activity and therefore does not belong in the traditional NSAID class of agents. It is speculated that SMPC contains natural factors that inhibit inflammation by suppressing neutrophil emigration from the vascular space, possibly by restricting extravasation through tight junctions.

The purpose of this study was to determine whether the antiarthritic effects of this nutraceutical supplement as described in human patients would be applicable to dogs. The trial was designed not only to test the product but also to evaluate and compare a standardized disability questionnaire with a case-specific questionnaire designed specifically for dogs, which came to be known as the “Cincinnati Orthopedic Disability Index” (CODI).

**MATERIALS AND METHODS**

**Test Population**

Five companion animal veterinary practices in the Cincinnati area participated in the randomized, parallel, double-blind, placebo-controlled trial that included outpatient dogs with musculoskeletal impairments. Fifty older, large-breed dogs of either sex were recruited based on the presence of disabilities observed by the owners. Physical examinations were performed by an attending veterinarian to rule out nonmusculoskeletal causes. Dogs with concomitant diseases that required treatment with drugs with overlapping effects (such as corticosteroids, NSAIDs, or analgesics) and dogs that were overly obese (in the opinion of the veterinarian) were excluded. To be eligible, the dogs had to be cared for by attentive owners who gave informed consent and agreed to treat and observe their dogs over a 9-week period (including a 1-week placebo run-in period designed to assess the level of compliance by the owners before the actual test materials were allocated).

**Treatments**

At the end of the placebo run-in period, treatments were assigned based on computer-generated random codes. Test and control articles were supplied in identical, coded plastic bottles. The test article was an SMPC powder (Micro-
Lactin, SMBI), described elsewhere, amongst supplied in gelatin capsules each containing 500 mg SMPC. The placebo was rice flour, an inert ingredient identical in appearance to the test powder, supplied in identical capsules. Each dog was given two capsules twice daily (2 g/day) for a total of 8 weeks. The first week of treatment after the run-in placebo period was designated Week 0. Neither the veterinarian nor the owner had knowledge of group assignments.

**Evaluations**

Blood samples were drawn at Week 0 and at the final visit and submitted for hematology and standard clinical chemistry profiles. Veterinary clinical evaluation consisted of history, medication review, and physical evaluation of lameness, weight bearing, joint mobility, and pain on manipulation according to published criteria. Clinical outcomes were based on physical examination, a standardized questionnaire on physical activities, a case-specific questionnaire developed with each owner (CODI), and owner and veterinarian global assessments of overall response to therapy (worse, no change, slight, good, excellent). Follow-up visits to the veterinary clinic were required at 4 and 8 weeks. To construct the CODI questionnaire, each owner was interviewed by the veterinarian or registered technician to determine the activities of the dog that appeared to be restricted by the musculoskeletal condition (Figure 1). Up to five observable activities were selected and then assessed by each owner biweekly throughout the study. If owners suggested more than five, they were asked to prioritize them and select the five activity restriction most egregious to either the owner or the dog. In addition to the CODI form, owners completed a standardized activity questionnaire biweekly (Figure 1).

At each visit, the owners were questioned about adverse events; study criteria and treatment records were reviewed; and unused capsules were counted as a compliance check. The owners were asked whether, in their opinion, the condition had improved (owner global assessment). At the final visit (Week 8), the above procedures were repeated and the final veterinary physical examination, veterinary global assessment, and laboratory tests were repeated.

**Statistical Evaluation**

The answers on the physical, standardized, and CODI forms were assigned numerical values 0 through 4 (normal to severe) and transformed to a scale (0 to 100), which has been used frequently in human orthopedics, using the following equation:

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

Owner and veterinarian global assessments were assigned numerical values of −1 (worse) to +3 (excellent). The data were analyzed using commercially available statistical software at the nominal .05 level of significance. The significance of any interaction between treatment and any particular clinic was tested by two-way analysis of variance (ANOVA) for the change from baseline for each outcome variable. Questionnaire data are ordinal rather than continuous, which implies nonparametric statistical treatment. The statistical significance of the changes in physical examination scores within each group was tested by the Wilcoxon signed rank test. Within group responses in standardized and case-specific disability scores and owners’ global assessments were tested by a Friedman repeated measures ANOVA on ranks test (a nonparametric equivalent to one-way ANOVA). Comparisons of responses between treatment and placebo groups were made by two-way repeated measures ANOVA with treatment and time as grouping variables. The strength of association (correlation) between
Cincinnati Orthopedic Disability Index (CODI)

Please tell us what activities seem to be difficult for your dog.

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

Now tell us which of these activities are most troublesome to you or your dog.

Changes or problems related to arthritis in your dog:

<table>
<thead>
<tr>
<th>Changes or problems related to arthritis in your dog:</th>
<th>no problem</th>
<th>a little</th>
<th>quite a bit</th>
<th>severe</th>
<th>impossible</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Standard Orthopedic Questionnaire

How difficult are these activities for your dog?

<table>
<thead>
<tr>
<th>How difficult are these activities for your dog?</th>
<th>no problem</th>
<th>a little</th>
<th>quite a bit</th>
<th>severe</th>
<th>impossible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Running</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jumping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Getting up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying down</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descending stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Owner questionnaire used to assess degree of disability in dogs with musculoskeletal impairments.
outcome variables was tested by the Spearman rank order correlation method applied to data from all 35 dogs that completed the study. Finally, the effect size (d), defined as the difference between the mean value in the test and placebo groups at the end of the trial divided by the standard deviation of the placebo outcome at trial end was computed for each outcome variable as follows:

\[
\text{Effect size} = \frac{\text{Change in mean treatment score} - \text{Change in mean placebo score}}{\text{SD change in placebo score}}
\]

RESULTS

Fifty dogs were enrolled, 35 of which completed the entire study. Of the 15 dogs that were removed from the study, six had been randomized into the SMPC group and nine were in the placebo group. Dropouts were due to various reasons, including perceived lack of efficacy, lost to follow up, or eliminated due to unrelated conditions such as fractures or noncompliance. Several common large breeds (e.g., shepherds, retrievers, boxers, Dobermans) were represented in the study, and both groups were similar in age, sex, and body weight distribution (Table 1). Each clinic contributed between five and 10 completed cases consisting of at least two dogs treated with placebo and two treated with SMPC. Because there was no significant treatment × clinic or treatment × sex interaction with regard to any outcome variable, the data were pooled for further analysis. Data obtained from questionnaires completed by owners for Weeks 2 and 6 were disregarded because some owners created new disabilities on their own or failed to score previously defined activities during those periods. No dogs were eliminated from the analysis based on these deviations. For the scoring systems to work properly, disabilities had to be present (acknowledged and recorded) at the start of the trial and monitored according to the given schedule.

Both treatments were well tolerated by the dogs with the exception of one placebo-treated and one SMPC-treated dog, each of which vomited within 30 minutes of each dosage and had to be withdrawn from the study. Hematology and serum chemistry results were essentially unchanged in both groups, with the exception of serum cholesterol, which decreased from a mean of 295 to 234 mg/dl in the SMPC group (P = .003) but did not change in the placebo group.

Global assessment of overall improvement was reported by owners in 12 of 18 dogs (66.7%) in the SMPC group and six of 17 dogs (35.3%) in the placebo group. The global assessments by veterinarians were in agreement with those of the owners for all dogs in the placebo group and in all but one dog in the SMPC group.

Numeric results of physical examinations, questionnaires, and owner and veterinarian global assessments are summarized in Table 2. At baseline, there were no significant differences be-

| TABLE 1. Sex, Age, and Body Weight Distribution for Arthritic Dogs Treated with Placebo or Special Milk Protein Concentrate (SMPC) |
| --- | --- | --- | --- |
| **Group** | **Dogs** | **Males** | **Females** | **Age (yr) [Range]** | **Body Weight (kg) [Range]** |
| Placebo | 17 | 7 | 10 | 9.9 ± 1.2 [8–12] | 32.4 ± 6.2 [19–41] |
| SMPC | 18 | 8 | 10 | 9.1 ± 1.7 [7–12] | 32.2 ± 7.7 [20–48] |

Age and weight data are expressed as mean ± SD.
al assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.

The most frequent case-specific impairments identified and monitored were long walks, difficulty on slippery floors, getting in and out of the car, apparent pain and stiffness during defecation, jumping onto furniture, retrieving toys, and playing with other animals. The standardized questionnaire results, which captured disabilities related to daily activities common to all dogs, were numerically higher than CODI disability parameters between treatment groups with regard to physical or questionnaire findings. Physical examination scores improved slightly (but significantly, \(P < .05\)) in both groups during the treatment period. Standardized and CODI scores and owner global assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.

The most frequent case-specific impairments identified and monitored were long walks, difficulty on slippery floors, getting in and out of the car, apparent pain and stiffness during defecation, jumping onto furniture, retrieving toys, and playing with other animals. The standardized questionnaire results, which captured disabilities related to daily activities common to all dogs, were numerically higher than CODI disability parameters between treatment groups with regard to physical or questionnaire findings. Physical examination scores improved slightly (but significantly, \(P < .05\)) in both groups during the treatment period. Standardized and CODI scores and owner global assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.

The most frequent case-specific impairments identified and monitored were long walks, difficulty on slippery floors, getting in and out of the car, apparent pain and stiffness during defecation, jumping onto furniture, retrieving toys, and playing with other animals. The standardized questionnaire results, which captured disabilities related to daily activities common to all dogs, were numerically higher than CODI disability parameters between treatment groups with regard to physical or questionnaire findings. Physical examination scores improved slightly (but significantly, \(P < .05\)) in both groups during the treatment period. Standardized and CODI scores and owner global assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.

The most frequent case-specific impairments identified and monitored were long walks, difficulty on slippery floors, getting in and out of the car, apparent pain and stiffness during defecation, jumping onto furniture, retrieving toys, and playing with other animals. The standardized questionnaire results, which captured disabilities related to daily activities common to all dogs, were numerically higher than CODI disability parameters between treatment groups with regard to physical or questionnaire findings. Physical examination scores improved slightly (but significantly, \(P < .05\)) in both groups during the treatment period. Standardized and CODI scores and owner global assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.

The most frequent case-specific impairments identified and monitored were long walks, difficulty on slippery floors, getting in and out of the car, apparent pain and stiffness during defecation, jumping onto furniture, retrieving toys, and playing with other animals. The standardized questionnaire results, which captured disabilities related to daily activities common to all dogs, were numerically higher than CODI disability parameters between treatment groups with regard to physical or questionnaire findings. Physical examination scores improved slightly (but significantly, \(P < .05\)) in both groups during the treatment period. Standardized and CODI scores and owner global assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.

The most frequent case-specific impairments identified and monitored were long walks, difficulty on slippery floors, getting in and out of the car, apparent pain and stiffness during defecation, jumping onto furniture, retrieving toys, and playing with other animals. The standardized questionnaire results, which captured disabilities related to daily activities common to all dogs, were numerically higher than CODI disability parameters between treatment groups with regard to physical or questionnaire findings. Physical examination scores improved slightly (but significantly, \(P < .05\)) in both groups during the treatment period. Standardized and CODI scores and owner global assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.

The most frequent case-specific impairments identified and monitored were long walks, difficulty on slippery floors, getting in and out of the car, apparent pain and stiffness during defecation, jumping onto furniture, retrieving toys, and playing with other animals. The standardized questionnaire results, which captured disabilities related to daily activities common to all dogs, were numerically higher than CODI disability parameters between treatment groups with regard to physical or questionnaire findings. Physical examination scores improved slightly (but significantly, \(P < .05\)) in both groups during the treatment period. Standardized and CODI scores and owner global assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.

The most frequent case-specific impairments identified and monitored were long walks, difficulty on slippery floors, getting in and out of the car, apparent pain and stiffness during defecation, jumping onto furniture, retrieving toys, and playing with other animals. The standardized questionnaire results, which captured disabilities related to daily activities common to all dogs, were numerically higher than CODI disability parameters between treatment groups with regard to physical or questionnaire findings. Physical examination scores improved slightly (but significantly, \(P < .05\)) in both groups during the treatment period. Standardized and CODI scores and owner global assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.

The most frequent case-specific impairments identified and monitored were long walks, difficulty on slippery floors, getting in and out of the car, apparent pain and stiffness during defecation, jumping onto furniture, retrieving toys, and playing with other animals. The standardized questionnaire results, which captured disabilities related to daily activities common to all dogs, were numerically higher than CODI disability parameters between treatment groups with regard to physical or questionnaire findings. Physical examination scores improved slightly (but significantly, \(P < .05\)) in both groups during the treatment period. Standardized and CODI scores and owner global assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.

The most frequent case-specific impairments identified and monitored were long walks, difficulty on slippery floors, getting in and out of the car, apparent pain and stiffness during defecation, jumping onto furniture, retrieving toys, and playing with other animals. The standardized questionnaire results, which captured disabilities related to daily activities common to all dogs, were numerically higher than CODI disability parameters between treatment groups with regard to physical or questionnaire findings. Physical examination scores improved slightly (but significantly, \(P < .05\)) in both groups during the treatment period. Standardized and CODI scores and owner global assessments improved significantly \((P < .01)\) in the test group but not in placebo controls. Comparisons between groups revealed that mean responses in the SMPC group were significantly \((P < .05)\) greater than in the placebo group with regard to CODI scores and owner global assessments, whereas physical examination and standardized questionnaire results and veterinarian global assessments did not differ statistically between groups.
dogs in the SMPC group at the final evaluation time were numerically similar to those of owners but not significantly different from placebo controls, as illustrated in Figure 3. Global assessments were significantly ($P < .001$) correlated with changes in physical examination and questionnaire scores, and all outcome variables were significantly correlated ($P < .001$) with each other (Table 3).

The effect sizes were 0.03, 0.62, 1.61, 0.90, and 0.65 for physical examination, standardized, case-specific, client global, and veterinarian global outcome variables, respectively. According to published orthopedic standards, these findings indicate that treatment had a large effect on case-specific and owner global responses, an intermediate effect on standardized and veterinarian global responses, and a negligible effect on the physical examination responses (Figure 4).

**DISCUSSION**

This prospective, randomized study was designed to examine the effect of a dietary nutraceutical supplement on disabilities of musculoskeletal origin that were of concern to the dog owner rather than to examine its effects on osteoarthritis per se. The hypothesis was that the attentive dog owner is capable of assessing treatment effects in conditions for which there are no consistent objective outcome markers. To simplify the study, the dose of SMPC was extrapolated from results of laboratory animal studies and clinical findings in humans, and the population of dogs was restricted in body...

---

**Figure 3.** Overall global response (mean ± SEM) for arthritic dogs to treatment with special milk protein concentrate (SMPC) or placebo according to owners and veterinarians. Each dog was scored on a scale of −1 to 3 (worse to excellent).

**Figure 4.** Comparison of effect size ([treatment response – placebo response]/SD placebo response).
weight and age. In particular, dogs with a degree of obesity that could have compromised musculoskeletal evaluations were excluded. The use of a 1-week placebo run-in period was based on two considerations: First, owners would have to prove to themselves and to the veterinarian that they were motivated enough to give their dog two large capsules orally twice daily. Second, the owners would have an opportunity to observe the dog’s behavior in the context of filling out score sheets and to rethink the case-specific disabilities to be monitored. Because the study was completely blinded, neither the owner nor the attending veterinarian was aware that only placebo capsules were given during that first week. The physical examination and questionnaire scores from Week 0 were used as baseline data.

The 35% placebo effect based on both owner and veterinarian global assessment of overall response appears high but is within the range of 25% to 38% placebo response reported in larger trials on the NSAID carprofen in dogs with osteoarthritis.5,28 Placebo effects must be attributed largely to owner or veterinarian expectations rather than to psychological effects on the canine patient. The finding that physical examination scores improved in both placebo and active groups is difficult to explain. Moreover, although physical findings did not differ, the veterinarian global assessments were higher for the test group than for controls, suggesting that veterinarians based their evaluations on factors other than changes in physical examination findings and were influenced in some manner by the owners. Numerically, the perceived difference in response between test product and placebo was greater for the owners than for the veterinarians (Figure 3), a finding consistent with results of other trials.5,29–31

Owner assessment of treatment outcome in orthopedics has been used successfully by other researchers to evaluate drugs and surgical procedures5,29,30,32,33 but has been less successful in evaluating nutraceuticals.34 Validated, questionnaire-based outcome measures consisting of 20 or more questions grouped into categories such as pain, stiffness, and activities of daily living have been used for some years in human arthritis trials.12,13,16,25 Dogs, however, cannot fill out questionnaires or be interviewed, and only seven activities could be identified that most dogs do on a daily basis for inclusion in the standardized questionnaire (the WOMAC approach). There was no attempt to categorize these questions, although others have monitored subcategories such as the dog’s quality of life, activity, lameness, disability, stiffness, ability to jump, and effect of cold, damp weather.26,30,32 Instead, a case-specific method was devised similar to the MACTAR approach proposed for human patients with rheumatoid arthritis13 (the CODI approach). In this initial trial, the specific disabilities were not ranked or weighted as is done in the original MACTAR approach, although this may have further improved sensitivity. The standardized

<p>| TABLE 3. Spearman Rank Order Correlation Coefficients in 35 Arthritic Dogs. All Outcome Variables are Highly Significantly Correlated ($P &lt; .001$) |
|---------------------------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Case-Specific</th>
<th>Client Global</th>
<th>Veterinarian Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>0.579</td>
<td>0.533</td>
<td>0.716</td>
<td>0.742</td>
</tr>
<tr>
<td>Standard</td>
<td>0.599</td>
<td>0.601</td>
<td>0.547</td>
<td></td>
</tr>
<tr>
<td>Case-specific</td>
<td></td>
<td>0.725</td>
<td>0.589</td>
<td>0.839</td>
</tr>
<tr>
<td>Client global</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veterinarian global</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
scores were invariably higher at baseline than the CODI scores because some of the individual standardized variables, such as walking and running, were often completely normal. For example, although a dog may not have difficulty walking or running, he may be unwilling to go for long walks, retrieve toys, or play with other animals. By capturing these details in case-specific questionnaires, the sensitivity of detecting owners’ perceptions of treatment effects is greatly enhanced. Although the CODI approach greatly improved sensitivity compared with the standardized approach in this study (Figure 3), both outcome measures were highly significantly correlated ($P < .001$) with owners’ global assessment scores.

There are several advantages to transforming subjective, ordinal data to the scale of 0 to 100, which is common in orthopedics, and broader utilization of this technique in veterinary trials is advocated by the authors. First, the transformed data often satisfy the criteria of normal distribution and equal variance that arguably justify the more-familiar, parametric statistical treatment. Second, the data from any subjective scoring system, regardless of the scale, can be similarly transformed and grouped into clinically meaningful categories such as stiffness, lameness, or activity. Well-defined scoring systems both in orthopedics and in other areas such as atopic dermatitis in dogs have been developed, and the data from these could easily be transformed to permit comparisons among treatment groups and various subgroups in similar terms. Third, use of the transformed scale establishes the custom of expressing clinical improvement in terms of increasing scores and enables calculation of percentage improvement by simple subtraction.

The concept of “effect size,” a unitless measure of the degree to which the apparent treatment effect exceeds the placebo effect, has not been widely reported in veterinary trials. Originally developed for the behavioral sciences, an effect size of 0.2 or below is considered a “small” effect, and 0.8 or higher is a “large” effect. According to this convention, the effect sizes on the CODI scale and the owner global assessment were large; the standardized scale and veterinarian global assessment were intermediate; and the physical examination outcome was negligible (Figure 4) in this study. It is also noted that the effect size on the CODI scale was markedly greater than on the other outcome measures. Calculation and reporting of effect size in veterinary trials is advocated as a convenient construct for comparing the magnitude of outcomes within and among trials.

In this first trial, it was anticipated that owners would be able to identify five or more disabilities unique to their pet. In fact, most owners only identified two or three concerns, and some of these were the same as those on the standardized form. It appears that more extensive owner interviews using probing questions such as “does your dog like to chase things?” or “do you take your dog on walks or outings?” would be more productive. Furthermore, it was concluded that the ability of the client and his or her rapport with both the dog and the veterinarian (or technician) are the most important aspects of case selection in such trials. Owners sometimes failed to list and score the same disabilities on follow-up forms or to list different ones as they were observed throughout the study. This was often true on home follow-up forms for Weeks 2 and 6, causing data from those times to be unreliable and therefore dropped from the study evaluation. To avoid this pitfall, it is important to write down the disabilities identified at baseline on all follow-up forms in advance. Forms for each evaluation period were deliberately issued separately in this study to encourage the owners and veterinarians to record the scores independent of previous ratings. Despite the shortcomings, the present
CODI methodology was of sufficient sensitivity to detect treatment effects, with adequate statistical power, in a relatively small study.

The paucity of adverse effects and lack of changes in clinical chemistry findings over the 8-week treatment period is noteworthy (but not unexpected) because the test substance is a naturally derived nutritional product, not an NSAID. The apparent serum cholesterol-lowering effect of the test product is of interest, not for its clinical relevance in dogs but rather because it is consistent with similar findings in human patients with hypercholesterolemia.37,38

In summary, this study describes the development of a scoring system for controlled clinical trials in dogs that is based on owner evaluation and permits the reduction of data derived in this manner to quantitative terms. Furthermore, the study demonstrated the value of the 0 to 100 transformed scale and the calculation and reporting of effect size in randomized, controlled trials in veterinary medicine. Results of the present trial using this methodology support the conclusion that the milk-derived SMPC ingredient has therapeutic value in dogs, and it provided benefits similar to those observed clinically in human patients using the same ingredient and similar methodology.23,24 Because the product does not share the mechanism or potential toxicity of NSAIDs,39 it appears to provide the veterinarian with a safe alternative for long-term management of musculoskeletal disabilities in aging pets. The results of this study are encouraging and provide justification for larger controlled trials in more diverse populations as well as trials to validate the present methodology against accepted objective standards.

ACKNOWLEDGMENTS

The authors thank the following Cincinnati area practitioners and their technicians for contributing clinical cases: Dr. Larry Smith, Salt Run Veterinary Clinic; Drs. Gary Schroeder, Mary Kelley, and Deborah McArthur, Peach Grove Animal Hospital; Drs. Richard Seaman and Lisa McMahan, Madeira Veterinary Hospital; Drs. Gary Smith, Robert Outzs, Pamela Sawyer, and Jack Walkenhorst, County Animal Hospital; Drs. Kevin Ketting, Terri McCarty, and Joseph Stratman, College Hill Pet Clinic. The authors also thank Dr. William Rogers, Veterinary Internal Medicine, for assistance in the original design of the study.

REFERENCES