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Therapeutic efficacy of undenatured type-II collagen (UC-II) in comparison to glucosamine and chondroitin in arthritic horses[1]

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The present investigation evaluated arthritic pain in horses receiving daily placebo, undenatured type II collagen (UC-II) at 320, 480, or 640 mg (providing 80, 120, and 160 mg active UC-II, respectively), and glucosamine and chondroitin (5.4 and 1.8 g, respectively, bid for the first month, and thereafter once daily) for 150 days. Horses were evaluated for overall pain, pain upon limb manipulation, physical examination, and liver and kidney functions. Evaluation of overall pain was based upon a consistent observation of all subjects during a walk and a trot in the same pattern on the same surface. Pain upon limb manipulation was conducted after the walk and trot. It consisted of placing the affected joint in severe flexion for a period of 60 sec. The limb was then placed to the ground and the animal trotted off. The response to the flexion test was then noted with the first couple of strides the animal took. Flexion test was consistent with determining clinically the degree of osteoarthritis in a joint. Horses receiving placebo showed no change in arthritic condition, while those receiving 320 or 480 or 640 mg UC-II exhibited significant reduction in arthritic pain ($P < 0.05$). UC-II at 480 or 640 mg dose provided equal effects, and therefore, 480 mg dose was considered optimal. With this dose, reduction in overall pain was from 5.7 ± 0.42 (100%) to 0.7 ± 0.42 (12%); and in pain upon limb manipulation from 2.35 ± 0.37 (100%) to 0.52 ± 0.18 (22%). Although glucosamine and chondroitin treated group showed significant ($P < 0.05$) reduction in pain compared with pretreated values, the efficacy was less compared with that observed with UC-II. In fact, UC-II at 480 or 640 mg dose was found to be more effective than glucosamine and chondroitin in arthritic horses. Clinical condition (body weight, body temperature, respiration rate, and pulse rate), and liver (bilirubin, GGT, and ALP) and kidney (BUN and creatinine) functions remained unchanged, suggesting that these supplements were well tolerated.

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INTRODUCTION

Arthritis is a chronic debilitating disease that commonly inflicts millions of horses around the world, because of excessive running and exercise, injury, immune disorder, aging, or genetic predisposition (Ruggeiro, 2002). The two most common types of arthritis are osteoarthritis and rheumatoid arthritis. In horses, osteoarthritis occurs with a greater frequency than rheumatoid

arthritis or any other form of joint disease, like in humans and dogs. Osteoarthritis is an inflammatory joint disease, which is characterized by degeneration of the cartilage, hypertrophy of bone at the margins, and changes in the synovial membrane and fluid, which eventually leads to pain and stiffness of joints (Goldring, 2000; Bellamy *et al.*, 2001). This disease can wear down cartilage in a joint to the point that bone rubs against bone, resulting in loss of cartilage, and, in severe cases, cartilage fragments can break off and irritate muscles with pain that are adjacent to the bone. Chronic joint inflammation usually results in progressive joint destruction, deformity, and loss of function (van Roon *et al.*, 2001).

Current therapy of arthritis relies upon nonsteroidal anti-inflammatory drugs (NSAIDs) alone or in combination with some other pain killers. Present treatments aim at alleviating pain, control inflammation, and preserve ability to perform daily functions. NSAIDs, which are cyclooxygenase (COX) inhibitors, alleviate pain, but do not eliminate signs and symptoms of active disease. In general, COX-II inhibitors (such as rofecoxib, celecoxib, carprofen, and deracoxib) are considered safer than nonspecific COX inhibitors (such as aspirin and ibuprofen). In the recent past, chronic use of COX-II inhibitors has been attributed to various side effects, including gastrointestinal (GI) ulceration and bleeding, and hepatic, renal and cardiovascular complications (Richardson, 1991; PDR, 2006; Infante & Lahita, 2000; Matteson, 2000; Schuna & Megeff, 2000; Matheson & Figgilt, 2001; Lamarque, 2004; Solomon *et al.*, 2004; Muhlfeld & Floege, 2005). To our knowledge, such side effects have not been reported in horses.

Presently, nutraceuticals are also used to ease the pain and discomfort of arthritis in both humans and animals, including horses (Trumble, 2005; Clegg *et al.*, 2006; Bruyere & Reginster, 2007; Morva, 2007). These products are commonly used in horses because they are administered orally, well tolerated and considered safe. Nutraceuticals are defined as functional foods, natural products, or parts of food that provide medicinal, therapeutic, or health benefits, including the prevention or treatment of disease. The present investigation utilized three supplements (UC-II, glucosamine, and chondroitin), and their brief description is provided here. Glycosylated undenatured type-II collagen (UC-II) is derived from chicken sternum and prepared under good manufacturing practices (GMPs), using low temperature, which preserves its undenatured form and ensures intact biological activity with active epitopes. Glucosamine, extracted from crab, lobster, or shrimp shells, is an amino-monosaccharide precursor of the disaccharide unit of glycosaminoglycan, which is the building block of proteoglycans, the ground substance of cartilage (Paroli *et al.*, 1991). Chondroitin sulfate, extracted from animal cartilage, such as tracheas and shark cartilage, is a part of a large protein molecule (proteoglycan) that gives cartilage elasticity.

Currently, glucosamine and chondroitin are the two most commonly used nutraceuticals in humans as well as in animals (including dogs, cats, and horses), to alleviate pain associated with arthritis (Dechant *et al.*, 2005; Trumble, 2005). However, based on recent randomized controlled trials and meta-analysis, these supplements have shown only small-to-moderate symptomatic efficacy in human osteoarthritis (Bruyere & Reginster, 2007), although, this finding is still debated (Clegg *et al.*, 2006; Rozendaal *et al.*, 2008). In our recent studies conducted in dogs, daily administration of UC-II at 40 mg (providing 10 mg active UC-II, respectively) daily dose for 120 days markedly reduced arthritic pain (DeParle *et al.*, 2005; D'Altilio *et al.*, 2007). Furthermore, our follow up studies also demonstrated that UC-II (40 mg daily dose) in combination with other nutraceuticals (glucosamine plus chondroitin) markedly reduced the signs associated with arthritis in dogs, and thereby, tremendously improved daily activity, as climbing stairs and walking exercise. In a number of *in vivo* and *in vitro* investigations, glucosamine and chondroitin have been found very effective against osteoarthritis in horses (Fenton *et al.*, 2000, 2002; Dechant *et al.*, 2005; Neil *et al.*, 2005; Trumble, 2005). In brief, these studies suggested that the combination of glucosamine and chondroitin appears to be more effective in preventing or treating osteoarthritis in horses than either product alone.

The present investigation was therefore undertaken with two specific objectives: (i) to determine if daily administration of active UC-II, or glucosamine plus chondroitin, can alleviate the signs and symptoms of arthritis in horses and (ii) to determine if these supplements are well tolerated and safe to administer for the long term in arthritic horses.

MATERIALS AND METHODS

Animals

All horses used in this investigation were diagnosed with osteoarthritis at the level of moderate severity. They were placed at the equine center of Murray State University. During the entire course of investigation, these horses were under the supervision of licensed veterinarians. The protocol of the present investigation for using arthritic horses and their treatment was in compliance with the Murray State University Animal Use and Care Guidelines. All animals were used routinely in their daily workout schedule (riding classes). They were lodged into the amount of time for daily workouts and rest periods. All animals had the same workout protocol and rest time.

Criteria for inclusion into the study

From a large pool of horses located at the Murray State University Equine Center, candidates were chosen based upon outward visual signs of lameness. Once the lame candidates were identified, the animals with evidence of osteoarthritis based upon physical examination by two licensed veterinarians (Dr. Terry D. Canerdy and Dr. William DeWees) were included in the study. Evidence of osteoarthritis includes joint effusion in one or more joints of the limbs, reduced joint flexibility, crepitation of the joint on manipulation, and an increase in lameness upon flexion of the affected joint.

Supplements

Glycosylated undenatured type-II collagen (UC-II), in the form of capsules as a dietary supplement, was provided by InterHealth Nutraceuticals, Inc. (Benicia, CA, USA). Similar to our previous studies conducted in dogs, in the present investigation, the undenatured form of glycosylated type-II collagen was used, as this form of UC-II is found to be significantly more effective than denatured type-II collagen against arthritis (Nagler-Anderson *et al.*, 1986; Bagchi *et al.*, 2002). It should be noted that undenatured type-II collagen can be denatured (hydrolyzed) by chemical or high-temperature, altering its molecular structure and integrity, and denatured collagen does not have active epitopes rendering it inactive. Cosequin equine powder concentrate (glucosamine and chondroitin) was purchased from Nutramax (Edgewood, MD, USA).

Experimental design and animal treatment

The present investigation was conducted on moderately osteoarthritic horses. In preliminary dose-dependent studies, horses received UC-II at 80 or 160 mg (providing 20 and 40 mg active UC-II, respectively) daily dose for a period of 150 days. Based on this pilot dose-dependent study, the final investigation was carried out on five groups of horses (n = 5–6) receiving placebo, UC-II (higher doses), or glucosamine in combination with chondroitin daily for 150 days. Group-I horses received placebo. Horses in Group-II, -III, and -IV received UC-II at 320, 480, and 640 mg (providing 80, 120, and 160 mg active UC-II, respectively), accordingly. Group-V horses received glucosamine and chondroitin (5.4 and 1.8 g/day, respectively, bid for the first month, and once daily thereafter). Treatment in all five groups was given daily (in the form of capsules administered orally in a handful of grain) for a period of 5 months. While rationale for selection of doses of UC-II was based on preliminary studies, doses of glucosamine and chondroitin were based on the product information provided on the insert along with Cosequin (Nutramax).

Pain assessment

The horses were evaluated for overall pain and pain after limb manipulation, on a monthly basis for a period of 150 days. Overall pain evaluation was based upon a consistent observation of all subjects when the animal was at a walk and a trot. All subjects were moved in the same pattern on the same surface consistently. Gross pain measurement was done and recorded during the horses movement trials.

Pain upon limb manipulation was conducted after the walk and trot. It consisted of placing the affected joint in severe flexion for a period of 60 sec. The limb was then placed to the ground and the animal trotted off. The response to the flexion test was then noted with the first couple of strides the animal took. Flexion test was consistent with determining clinically the degree of osteoarthritis in a joint. With an increase in osteophytes, the animal has a degree of discomfort on movement of the limb following flexion. Flexion tests are commonly used in the equine industry in determining the severity of a joint abnormality.

Scale used in pain measurement

The 0–10 global pain assessment was a scale used because it provided a broad range of scale for pain. This scale was consistently used throughout the investigation. In brief, 0, no pain; 5, moderate pain; and 10, severe and constant pain. To our knowledge, a universal scale does not exist to assess the pain.

For pain upon limb manipulation, results were graded on a scale of 0–4: 0, no pain, 1, mild pain; 2, moderate pain; 3, severe pain; and 4, severe and constant pain. The 0–4 scale was taken from the American Association of Equine Practitioners (AAEP) scorecard on lameness. They actually have 0–5, but category 5 was dropped because it indicates inability of an animal to move. None of our subjects fit this category and therefore it was not used.

Physical examination

Body weights and physical evaluation were also determined on a monthly basis for 150 days. On a monthly basis horses were evaluated for body weight, body temperature, and pulse rate.

Biochemical assays

Blood samples were collected by jugular venipuncture using 20-gauge needles and 12-cc syringes. Serum was separated in a marble top tube (without anticoagulant) and transferred into plastic snap-top tubes. Serum samples were frozen immediately and kept at −80 °C until analyzed for bilirubin, GGT, ALP, blood urea nitrogen (BUN) and creatinine, using Beckman Coulter CX5-PRO Synchron Clinical System (Fullerton, CA, USA). Bilirubin, GGT, and ALP were used as markers of liver function, and BUN and creatinine were used as markers of renal function.

Statistical analysis

The data of body weight in Table 1, serum chemistry in Table 2, and pain measurement in Figs 1 & 2, are presented as means ± SEM. Statistical significance of differences was determined by ANOVA coupled with Tukey–Kramer test using the NCSS 2000 Statistical Software for Windows (Kaysville, UT, USA). Groups were compared using Duncan's Multiple-Comparison Test. Differences with $P < 0.05$ were considered statistically significant.

RESULTS

Horses used in this investigation were diagnosed with osteoarthritis at a moderate severity. They exhibited some of the common symptoms, such as difficulty during walking, stiffness after periods of inactivity, swelling/tenderness in one or more joints, steady pain in joints, and lameness.

Table 1. Effect of UC-II or Glucosamine plus Chondroitin on body weight (lbs) of horses

Day	Group-I placebo	Group-II 320 mg UC-II	Group-III 480 mg UC-II	Group-IV 640 mg UC-II	Group-V Gluc. + Chon.
0	1161 ± 40 (100)	1080 ± 18 (100)	1150 ± 59 (100)	1190 ± 48 (100)	1195 ± 30 (100)
30	1172 ± 16 (101)	1070 ± 23 (99)	1147 ± 58 (100)	1200 ± 45 (101)	1204 ± 27 (101)
60	1151 ± 48 (99)	1066 ± 22 (99)	1127 ± 53 (98)	1164 ± 49 (98)	1178 ± 33 (99)
90	1131 ± 43 (98)	1068 ± 21 (99)	1137 ± 56 (99)	1178 ± 42 (99)	1185 ± 34 (99)
120	1053 ± 28 (90)	1069 ± 17 (99)	1150 ± 66 (100)	1203 ± 47 (101)	1190 ± 31 (100)
150	1080 ± 39 (93)	1082 ± 23 (100)	1102 ± 59 (96)	1167 ± 33 (98)	1195 ± 49 (100)

Values are means ± SEM (n = 5–7). No significant change in body weight ($P > 0.05$). Numbers in parentheses are percent changes compared with values of day 0 (100%).

Table 2. Effects of UC-II or glucosamine plus chondroitin on markers of liver and renal functions in serum of horses

		Days					
Parameters	Group	0	30	60	90	120	150
BIL (mg/dL)	I	1.18 ± 0.12	1.24 ± 0.12	1.22 ± 0.17	1.34 ± 0.19	1.22 ± 0.16	1.34 ± 0.11
	II	1.33 ± 0.10	1.60 ± 0.06	1.70 ± 0.04	1.30 ± 0.09	1.30 ± 0.03	1.20 ± 0.10
	III	0.98 ± 0.13	1.05 ± 0.13	1.05 ± 0.09	1.15 ± 0.19	1.63 ± 0.27	1.17 ± 0.14
	IV	0.93 ± 0.14	0.77 ± 0.12	1.05 ± 0.12	1.04 ± 0.12	1.30 ± 0.16	0.93 ± 0.10
	V	1.87 ± 0.35	1.84 ± 0.43	1.76 ± 0.27	1.87 ± 0.37	2.07 ± 0.36	2.22 ± 0.48
GGT (IU/L)	I	12.4 ± 2.01	11.4 ± 1.21	11.2 ± 1.68	11.2 ± 1.39	11.8 ± 1.59	13.4 ± 1.21
	II	17.5 ± 9.51	15.4 ± 5.42	14.8 ± 4.82	15.3 ± 8.46	15.1 ± 11.32	14.5 ± 7.90
	III	14.2 ± 1.99	16.2 ± 1.90	13.0 ± 1.51	11.5 ± 1.06	12.7 ± 1.28	12.8 ± 1.35
	IV	14.8 ± 0.79	16.0 ± 0.52	13.1 ± 0.17	13.0 ± 0.58	14.5 ± 0.99	16.6 ± 1.50
	V	12.0 ± 0.69	11.7 ± 0.70	11.5 ± 1.31	12.1 ± 0.73	13.1 ± 0.37	12.1 ± 0.65
ALP (IU/L)	I	95.2 ± 9.61	90.2 ± 7.09	86.4 ± 7.42	94.2 ± 10.18	97.8 ± 14.65	95.4 ± 10.17
	II	79.4 ± 17.91	58.1 ± 22.97	81.3 ± 15.53	87.8 ± 19.38	84.3 ± 22.66	84.5 ± 30.80
	III	84.3 ± 8.50	73.2 ± 5.77	76.7 ± 5.71	74.7 ± 9.43	85.7 ± 12.46	88.3 ± 9.96
	IV	81.5 ± 3.33	68.5 ± 2.84	75.5 ± 3.23	72.8 ± 3.97	77.8 ± 3.66	97.5 ± 4.61
	V	82.6 ± 7.65	77.7 ± 3.98	62.6 ± 6.10	71.4 ± 4.50	75.2 ± 5.50	66.5 ± 7.70
BUN (mg/dL)	I	16.4 ± 0.87	13.6 ± 0.50	14.0 ± 0.89	16.4 ± 1.21	15.2 ± 1.43	18.0 ± 1.34
	II	17.7 ± 1.19	17.9 ± 1.12	17.3 ± 1.08	15.3 ± 1.19	15.1 ± 1.62	14.8 ± 2.00
	III	17.3 ± 1.50	17.1 ± 0.83	16.0 ± 0.86	15.8 ± 0.70	16.3 ± 1.23	18.8 ± 1.14
	IV	18.7 ± 0.88	14.2 ± 0.87	17.3 ± 0.91	19.0 ± 1.13	18.5 ± 0.43	18.8 ± 1.49
	V	18.5 ± 0.50	19.3 ± 0.92	18.9 ± 0.99	16.6 ± 1.74	18.0 ± 1.46	17.2 ± 1.32
Creatinine (mg/dL)	I	1.64 ± 0.08	1.58 ± 0.19	1.66 ± 0.08	1.46 ± 0.12	1.44 ± 0.14	1.66 ± 0.15
	II	1.50 ± 0.07	1.56 ± 0.07	1.51 ± 0.05	1.47 ± 0.07	1.50 ± 0.07	1.35 ± 0.07
	III	1.42 ± 0.06	1.43 ± 0.06	1.58 ± 0.12	1.33 ± 0.07	1.45 ± 0.04	1.48 ± 0.16
	IV	1.52 ± 0.06	1.48 ± 0.06	1.48 ± 0.05	1.30 ± 0.05	1.33 ± 0.02	1.30 ± 0.08
	V	1.43 ± 0.18	1.64 ± 0.19	1.39 ± 0.18	1.53 ± 0.17	1.50 ± 0.15	1.60 ± 0.23

Values are means ± SEM (n = 5–7). No significant change in any parameter ($P > 0.0.5$).

All horses were grossly and physically examined and flexed for lameness on a monthly basis for a period of 150 days. UC-II at a 320, 480, or 640 mg daily dose (providing 80, 120, or 160 mg active UC-II, respectively) provided significant reductions in arthritic pain by 60 days of treatment (Figs 1 & 2). In fact, with higher daily dose of UC-II (480 or 640 mg), significant reduction in overall pain was observed as early as after 30 days of treatment. With UC-II (320 or 480 or 640 mg), horses showed maximal pain reduction by 150 days of treatment (overall pain reduction, 79%, 88%, and 91%, respectively; and pain after limb manipulation, 71%, 78%, and 80%, respectively). After 5 months of UC-II treatment, the horses became very active, and performed normally in their daily activities.

Horses receiving glucosamine (5.4 g) plus chondroitin (1.8 g), bid for the first 30 days, and once daily, thereafter for the next 120 days showed significant decrease in pain after 60 days of treatment (reduction in overall pain, 36%; and reduction in pain after limb manipulation, 31%). Maximal pain reduction was noted after 150 days of treatment (overall pain, 68%; and pain after limb manipulation, 69%). On comparison, the UC-II (480 or 640 mg daily dose) was found to be approximately twice as effective as glucosamine plus chondroitin, based on pain after limb manipulation on day 90.

None of the horses in any group showed any adverse effects on body weight (Table 1), hepatic (bilirubin, GGT, and ALP) or renal (BUN and creatinine) function markers (Table 2), or body temperature, pulse rate, and respiration rate (data not shown), suggesting that these supplements are well tolerated by arthritic horses and safe to administer for a long term.

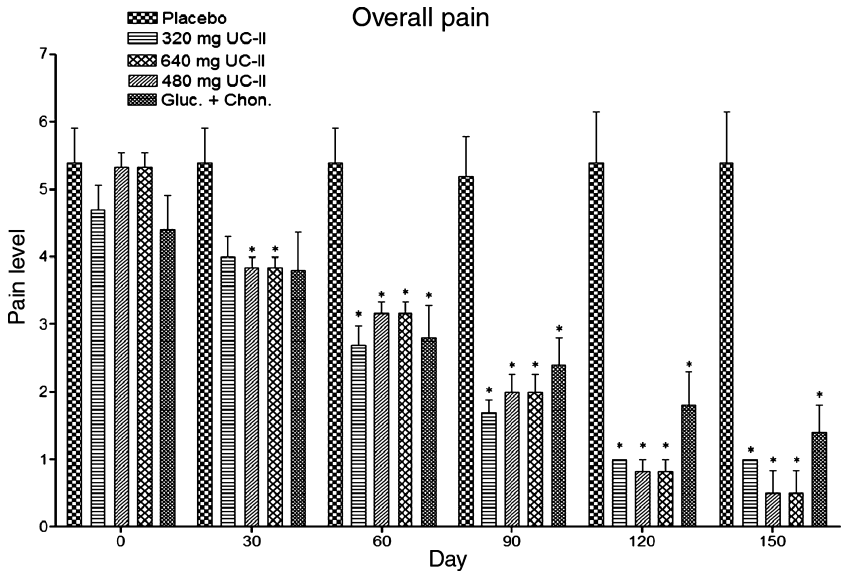

Fig. 1. On a monthly basis, overall pain in horses was measured as a general gross observation and graded on a scale of 0–10: 0, no pain; 5, moderate pain; and 10, severe and constant pain. Values are mean ± SEM (n = 5–7). * = Indicates significant difference between the values of day 0 and post-treatment ($P < 0.05$).

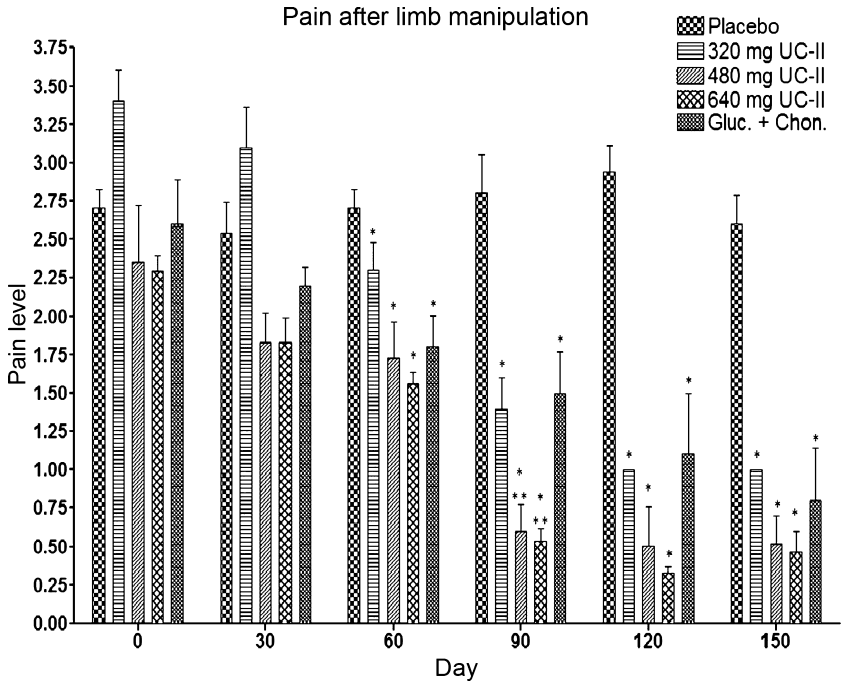

Fig. 2. On a monthly basis, pain upon limb manipulation was evaluated by animal's pain during the flexion of all four limbs for a min. then jogged after each leg was flexed. Results were graded on a scale of 0–4: 0, no pain; 1, mild pain; 2, moderate pain; 3, severe pain; and 4, severe and constant pain. Values are mean ± SEM (n = 5–7). *Significant difference between the values of day 0 and post-treatment ($P < 0.05$). **Significant difference between the values of UC-II-treated and glucosamine plus chondroitin-treated horses ($P < 0.05$).

DISCUSSION

The present investigation evaluated therapeutic efficacy, tolerability, and safety of glycosylated undenatured type II collagen (UC-II) and glucosamine and chondroitin in moderately arthritic horses, following a long term of their use. The present findings revealed that the therapy with UC-II at 320 or 480 or 640 mg daily dose for a period of 5 months provided significant improvement in ameliorating the overall pain and pain after limb manipulation in arthritic horses. Although significant anti-arthritic effects were noted after 60–90 days, the maximal physical improvements were observed after 150 days of treatment and the horses were more playful and active (Figs 1 & 2). This suggests that prolonged treatment with these supplements leads to better therapeutic results. Based on this study, it appears that 480 mg daily dose of UC-II provides the best results, as at further higher dose (640 mg providing 160 mg active UC-II), UC-II offered therapeutic efficacy no greater than that observed with 480 mg daily dose.

Like previous studies conducted in two monogastric species, humans (Nagler-Anderson *et al.*, 1986; Trentham *et al.*, 1993, 2001; Barnett *et al.*, 1996, 1998; Sieper *et al.*, 1996; Trentham, 1998) and dogs (DeParle *et al.*, 2005; D'Altilio *et al.*, 2007), in the horses, we used the undenatured form of UC-II. This form of collagen with triple helix structure and active epitopes is found to be significantly more effective than denatured form against

arthritis (Nagler-Anderson *et al.*, 1986; Bagchi *et al.*, 2002). In none of the species has UC-II been found to produce any adverse effects (Bagchi *et al.*, 2002; D'Altilio *et al.*, 2007), which demonstrated that once UC-II is ingested, stomach acids and enzymes perform a partial digestion of the collagen matrix, resulting in chains of soluble collagen molecules of varying length, containing biologically active epitopes. These structurally precise natural epitopes in UC-II interact with Peyer's Patches and trigger the complex series of immunological events that, in case of rheumatoid arthritis, down-regulates the body's out-of-control autoimmune response (Fig. 3) (Trentham *et al.*, 2001; Bagchi *et al.*, 2002). In the case of osteoarthritis, which is often characterized by a subclinical immune disorder and a vicious cycle of inflammatory events, UC-II can promote a significant reduction in inflammation (Bagchi *et al.*, 2002). UC-II functions through a process of oral tolerization that takes place in the small intestine where the food is absorbed. Through a complex series of immunological events, patches of lymphoid tissue (Peyer's Patches) surrounding the small intestine, screen incoming compounds and serve as a 'switch' to turn the body's immune response to foreign substances on or off, depending upon the substance. In dogs and humans, a small amount of undenatured UC-II (10 mg active UC-II/day) taken orally has been shown to turn off the immune response targeted at type-II collagen in joint cartilage, and no adverse effects have been noted (Trentham *et al.*, 1993, 2001; Trentham, 1998; DeParle *et al.*, 2005). This immunization process helps the body to differentiate between elements that are foreign invaders to the body and those that are nutrients and are good for the body (Weiner, 1997; Trentham, 1998). UC-II stops the immune system from attacking and damaging its own joint cartilage, thereby improving joint mobility and flexibility (Trentham *et al.*, 1993; Trentham, 1998; Bagchi *et al.*, 2002). Type-II collagen is one of the primary connective tissues of the body, providing flexibility and support to bone joints. As UC-II is found to be as equally effective in horses, as reported earlier in humans and dogs, and it is presumed that the mechanisms described for humans and dogs may also hold true for horses. Although the precise biochemical mechanism involved in UC-II- induced pharmacological anti-arthritic effects in humans, dogs or horses, is not clearly established.

Glucosamine and chondroitin (5.4 and 1.8 g, respectively, bid for the first 30 days, and once daily for the next 120 days) significantly reduced arthritic pain by 60 days of treatment (Figs 2 & 3), but maximal pain reduction was observed after 150 days (68% in overall pain and 69% in pain after limb manipulation). Recently, a number of *in vivo* and *in vitro* studies support the use of glucosamine and chondroitin in arthritic horses (Fenton *et al.*, 2000, 2002; Dechant *et al.*, 2005; Neil *et al.*, 2005; Trumble, 2005). Unlike UC-II, glucosamine relieves pain by enhancing proteoglycan synthesis, which is impaired in osteoarthritic cartilage (Hougee *et al.*, 2006). Chondroitin sulfate aids in keeping cartilage tissue from dehydrating and assists in cushioning impact stress and reducing joint pain. Chondroitin sulfate is also believed to block certain enzymes that result in the breakdown of cartilage. In an *in vitro* study, Dechant *et al.* (2005) demonstrated that glucosamine plus chondroitin: (i) reduced total glycosaminoglycan degradation, which is involved in osteoarthritis and (ii) have no detrimental effects on cartilage metabolism. Furthermore, from a series of *in vitro* studies, Fenton *et al.* (2000, 2002) revealed that glucosamine can prevent experimentally induced cartilage degradation, and therefore support the use of this product in prevention or treatment of cartilage loss in arthritic horses. In a recent *in vivo* study, glucosamine and chondroitin ameliorated arthritic pain in dogs, but comparatively UC-II was significantly more effective. Similarly, in horses UC-II (480 or 640 mg daily dose) was found to be more effective compared with glucosamine and chondroitin based upon limb manipulation on 90 days of treatment.

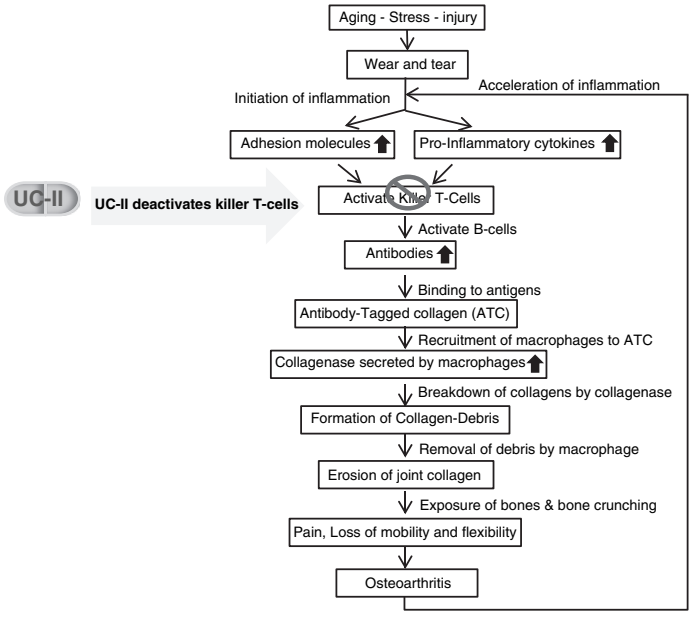

Fig. 3. Mechanism of action of UC-II in osteoarthritis.

In conclusion, daily administration of UC-II at varying doses (320 or 460 or 640 mg) significantly reduced the signs and symptoms of arthritis in horses. Daily administration of glucosamine plus chondroitin also provided reduction in arthritic pain, but the efficacy was less than UC-II. All three supplements were well tolerated and did not produce any adverse events.

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