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Therapeutic efficacy and safety of undenatured type-II collagen (UC-II) alone or in combination with (−)-hydroxycitric acid and chromemate in arthritic dogs[1]

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The present investigation evaluated therapeutic efficacy and safety of glycosylated undenatured type II collagen (active UC-II) alone or in combination with (−)-hydroxycitric acid (HCA-SX, SuperCitrimax) and ChromeMate (chromium niacinate, CM). Twenty five arthritic dogs in five groups ($n = 5$) received daily treatment as follows: group I (placebo), group II (10 mg active UC-II), group III (1800 mg HCA-SX), group IV (1800 mg HCA-SX + 100 μg CM), and group V (1800 mg HCA-SX + 100 μg CM + 10 mg active UC-II). The treatment was given daily for 120 days, followed by 30 days withdrawal. The dogs were evaluated for overall pain, pain upon limb manipulation, and exercise-associated lameness, on a monthly basis. Blood-serum samples were assayed for markers of liver [bilirubin and alanine aminotrasferase (ALT)] and renal [blood urea nitrogen (BUN) and creatinine] functions. Group I dogs exhibited no significant change in arthritic conditions. The dogs receiving active UC-II alone (group II) or in combination with HCA-SX + CM (group V) for 90 days showed marked reduction in overall pain (46–57%), pain upon limb manipulation (50–55%), and exercise-associated lameness (44–46%). In groups II and V, maximum pain reduction was seen after 120 days treatment (62–70%, 67–91%, and 69–78%, correspondingly). All dogs experienced a relapse of pain after a withdrawal period of 30 days. None of the dogs in any group showed adverse effects or changes in liver or kidney function markers, or body temperature. Body weights of all dogs remained significantly unchanged in all the groups. These data suggest that treatment of arthritic dogs with active UC-II alone or in combination with HCA-SX and CM ameliorates the signs of arthritis, and these supplements are well tolerated as no adverse effects were noted.

Arthritis is a chronic degenerative disease of the joints causing pain, stiffness, swelling, and lameness (McLaughlin, 2000; Burns, 2006). Arthritis commonly affects large breed dogs (Richardson *et al.*, 1997), because of overweight/obesity, lack of exercise, physical injury, aging, infection, immune disorder, or genetic predisposition. Dogs suffer more often with osteoarthritis than with rheumatoid arthritis (Hielm-Bjorkman *et al.*, 2003). Osteoarthritis is an inflammatory joint disease, which is characterized by degeneration of the cartilage, hypertrophy of bone at the margins in the synovial membrane, and eventually pain and stiffness of joints (Vaughan-Scott & Taylor, 1997).

Present therapy for arthritis in dogs relies upon drugs that alleviate pain and control inflammation to preserve daily activity. Chronic use of cyclooxygenase (COX) inhibitors (nonsteroidal anti-inflammatory drugs, NSAIDs) is linked to numerous side effects, including gastrointestinal (GI) bleeding, and hepatic and renal dysfunction (Lobetti & Joubert, 2000; Bergh & Budsberg, 2005). In the recent past, two commonly used FDA-approved drugs (Rimadyl and Deramaxx), which are NSAIDs and selective inhibitors of COX-II, have been shown to cause severe side effects (Moreau *et al.*, 2003; Sessions *et al.*, 2005).

In recent years, InterHealth Nutraceuticals, Inc. (Benicia, CA, USA) has developed three supplements (active UC-II, SuperCitrimax, and ChromeMate) that are proven to be very effective in human arthritis and/or obesity patients (Bagchi *et al.*, 2002;

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Soni *et al.*, 2004; Shara *et al.*, 2005). The structural integrity of undenatured type II collagen in a active UC-II sample was determined by Transmission Electron Microscope procedure using an EM JEOL 100 CX (Peabody, MA, USA), while the amount of undenatured type-II was analyzed by Capture ELISA kit (Chondrex LLC, Redmond, WA, USA) (Bagchi *et al.*, 2002).

Twenty-five client-owned arthritic dogs weighing between 62 and 96 pounds were used in this investigation. These dogs exhibited the signs of osteoarthritis (joint stiffness, lameness, pain, swollen joints, and difficulty in getting up or down and walking), which was confirmed radiographically. Dogs were randomly divided into five groups ($n = 5$) receiving daily treatment as follows: group I (placebo), group II (10 mg active UC-II), group III (1800 mg HCA-SX), group IV (1800 mg HCA-SX + 100 μg CM); and group V (1800 mg HCA-SX + 100 μg CM + 10 mg active UC-II). Daily treatment was given for 120 days, followed by a 30-day withdrawal.

Overall pain, pain upon limb manipulation, and lameness after physical exertion was measured on a monthly basis for a period of 150 days. Grading for pain measurement is described in figure legends (Figs 1–3), and in our recent publications (DeParle *et al.*, 2005; D'Altilio *et al.*, 2007).

Data of pain assessment are shown in Figs 1–3. Dogs receiving placebo showed no improvement in arthritic pain or lameness. Dogs receiving active UC-II alone showed significant reduction in overall pain, pain upon limb manipulation, and exercise-associated lameness. Maximum improvement was noted after 120 days of treatment. HCA-SX alone did not provide significant improvement in pain reduction, but in combination with CM, it provided significant reductions in arthritic signs, including pain. Active UC-II in combination with HCA-SX and CM markedly reduced overall pain (70%), pain upon limb manipulation (67%), and exercise-associated lameness (69%). Following a 30-day withdrawal, dogs experienced a relapse of pain and lameness. Data of dogs' body weight, body temperature, and serum chemistry related to liver and renal function (bilirubin, ALT, BUN, and creatinine), did not show any significant changes at 0, 30, 60, 90, 120, and 150 days.

Recently, in a double-blinded pilot study, we found for the first time that active UC-II (1 or 10 mg/day) given for 90 days significantly reduced the pain in arthritic dogs (DeParle *et al.*, 2005). Dogs given 10 mg active UC-II performed overall better than those given a 1-mg dose. In a follow-up study, dogs receiving active UC-II (10 mg/day) alone or in combination with Glucosamine HCl (2000 mg/day) and Chondroitin sulfate (1600 mg/day) for 120 days showed significant reductions in pain (D'Altilio *et al.*, 2007). The present data revealed that daily therapy with active UC-II alone or with HCA-SX + CM for 120 days provided remarkable improvements in the lifestyle of dogs by reducing arthritic pain. The majority of anti-arthritic effects appeared to be obtained from active UC-II, which exerts its effects through a process of oral tolerization (Trentham, 1998; DeParle *et al.*, 2005; D'Altilio *et al.*, 2007). Dogs receiving these supplements were more playful and showed significant reductions in the signalments of the arthritic condition, including pain and lameness (Figs 1–3).

In conclusion, arthritic dogs treated with active UC-II alone or in combination with HCA-SX and CM showed marked reductions in arthritic pain and lameness. Overall, the dogs became very active and playful. The supplements did not

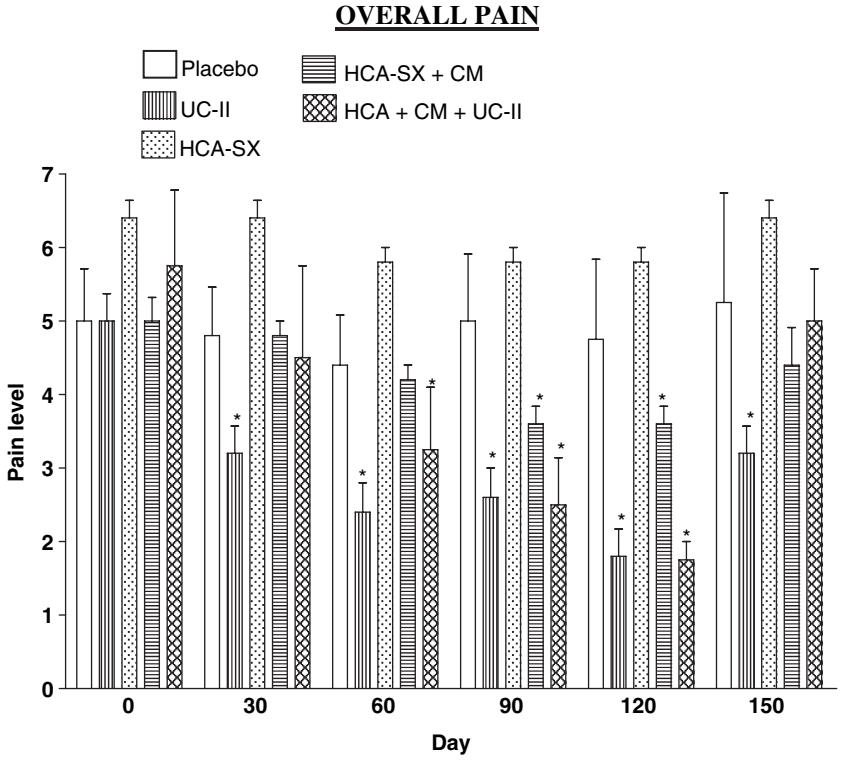

Fig. 1. Effects of active UC-II alone (10 mg/dog/day) or in combination with HCA-SX (1800 mg/dog/day) + CM (100 μg/dog/day) on overall pain in arthritic dogs ($n = 5$ dogs/group). Daily treatment continued for 120 days, followed by a withdrawal period of 30 days. Overall pain was graded on a scale of 0–10: 0, no pain; 5, moderate; and 10, severe and constant pain. For details, see the text and DeParle *et al.* (2005). *Significantly different when compared with pretreated values ($P < 0.05$). Active UC-II, glycosylated undenatured type-II collagen; HCA-SX, (−)-hydroxycitric acid; and CM, ChromeMate.

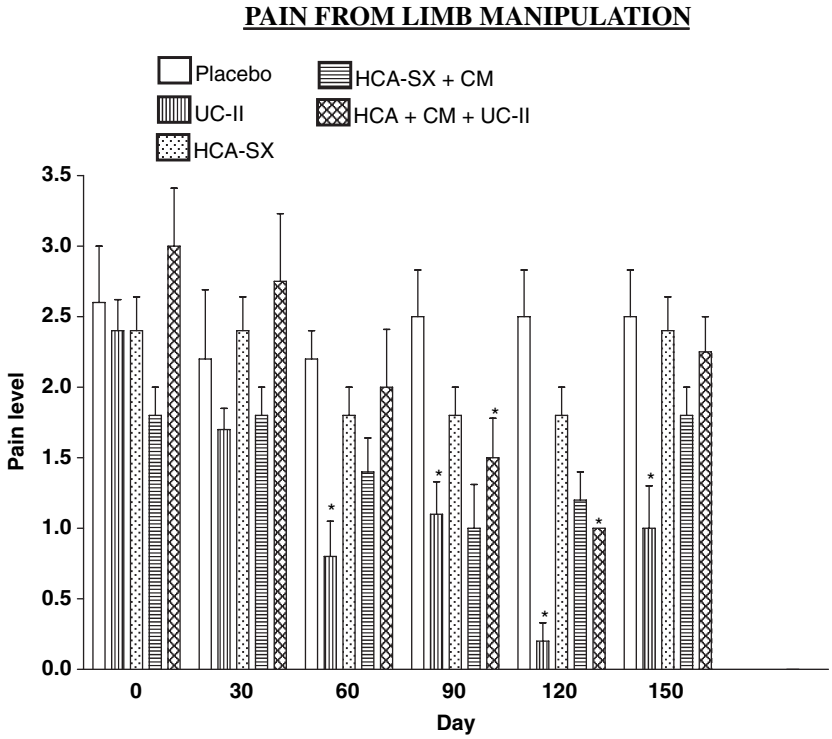

Fig. 2. Effects of active UC-II alone or in combination with HCA-SX + CM on pain after limb manipulation. Pain was evaluated by animal's vocalization or other observations of pain during the extension and flexion of all four limbs for few min. Pain was graded on a scale of 0–4: 0, no pain; 1, mild; 2, moderate; 3, severe; and 4, severe and constant pain. For details, see the text and Fig. 1. *Significantly different when compared with pretreated values ($P < 0.05$).

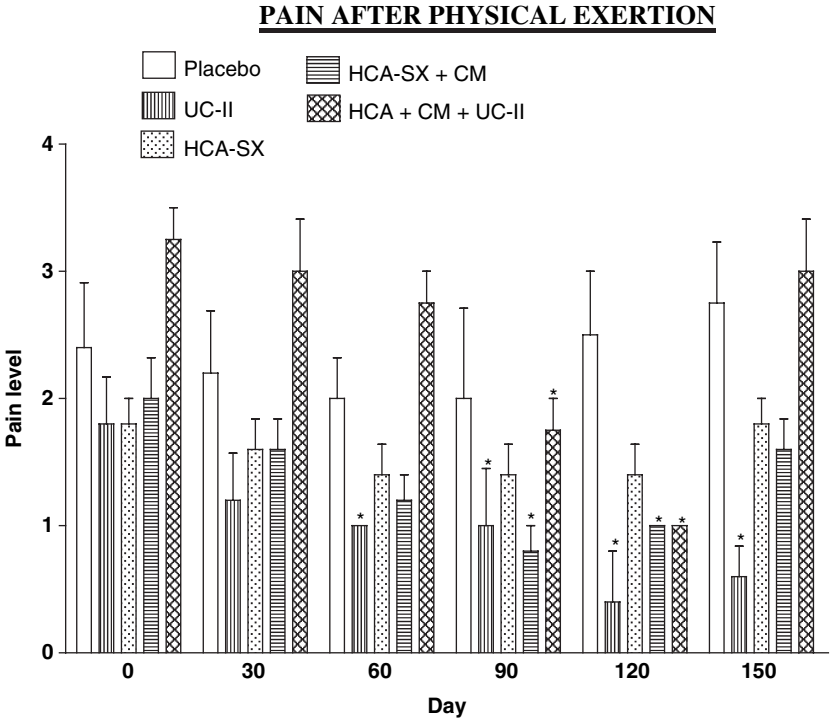

Fig. 3. Effects of active UC-II alone or in combination with HCA-SX + CM on pain after physical exertion. Lameness was measured after physical exercise for limping, holding limb up, rigidity of limbs, etc. Signs of pain and lameness were graded on the scale of 0–4: 0, no pain; 1, mild; 2, moderate; 3, severe; and 4, severe and constant pain. For details, see the text and Fig. 1. *Significantly different when compared with pretreated values ($P < 0.05$).

produce any side effects and were well tolerated. Relapse of arthritic signs, seen following a 30-day withdrawal, suggests that continuous therapy is needed. These data suggest that active UC-II, HCA-SX, and CM are well tolerated and safe to use with great efficacy in arthritic dogs.

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