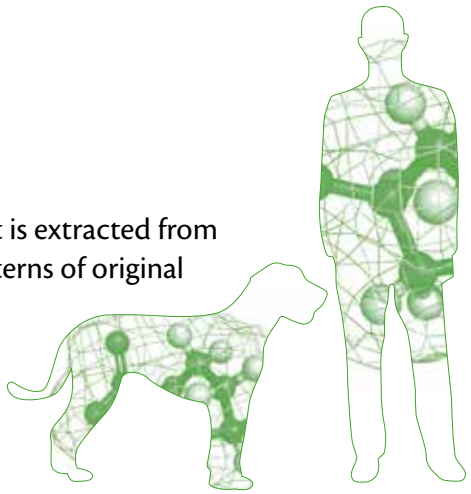
UC-II®



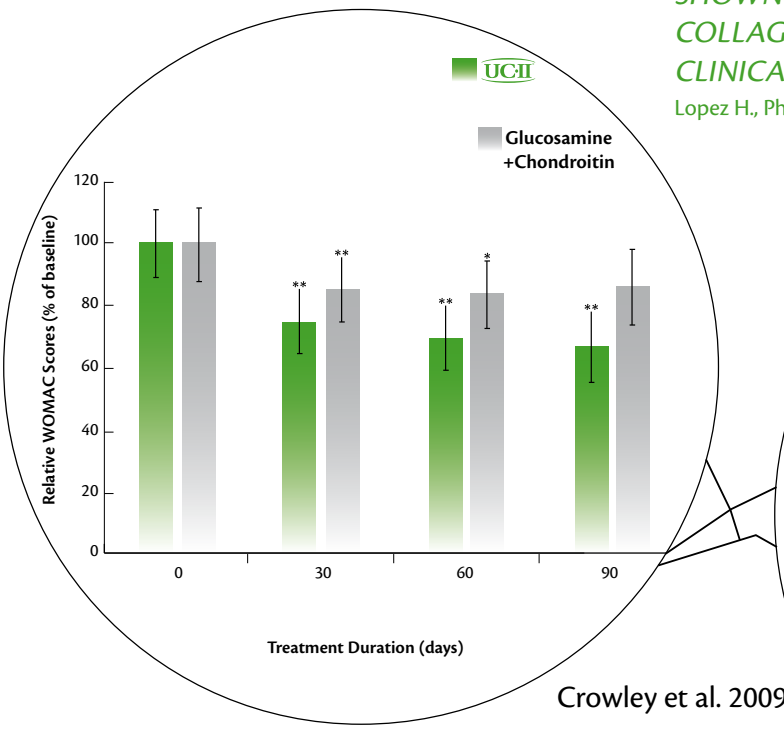
UC-II stands for undenatured type II collagen. This active but natural ingredient is extracted from chicken sternum. The unique and patented extraction process retains main patterns of original molecular structure of collagen II: triple helical helix, and glycosylated epitopes.

In humans, there are compelling proofs of safety and efficacy of this ingredient in rheumatoid arthritis (RA) and osteoarthritis (figures).

Mode of action is related to a local mechanism. In RA, there is a recognition in Payer's patches of the collagen epitopes. The epitopes positively influence the immunoregulatory response signaling required for the development of **immunotolerance** toward collagen.

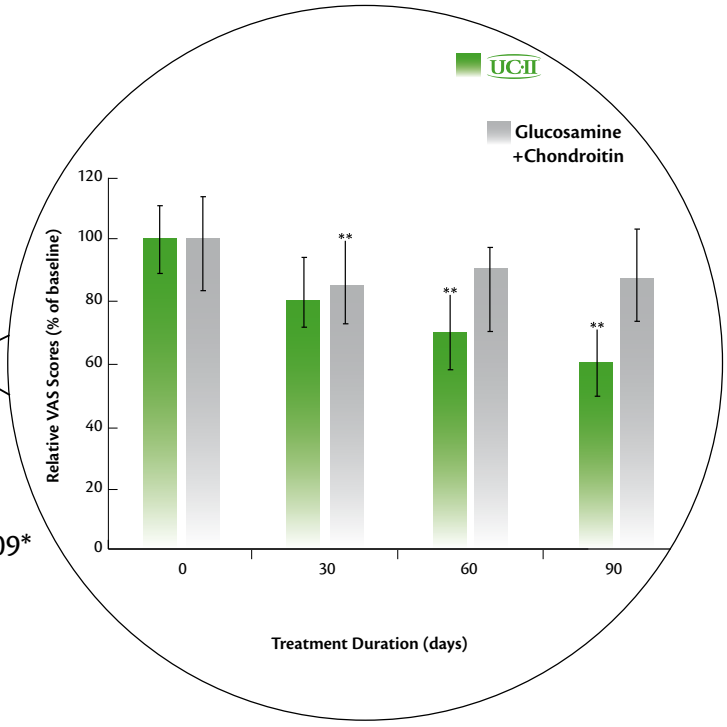
"NUMEROUS STUDIES IN ANIMAL MODELS OF OA HAVE SHOWN THE SUPERIORITY WITH UNDENATURED TYPE II COLLAGEN OVER GLUCOSAMINE AND CHONDROITIN IN CLINICAL SIGNS AND BIOMARKERS OF JOINTS"

Lopez H., Physical Medicine & Rehabilitation 2012 May;4(5 Suppl):S155-68 2012



Crowley et al. 2009*

Changes in WOMAC scores at day 90 from baselines. WOMAC scores from each treatment group were compared to baseline value at specified time points. Each bar presents mean +/- SEM. *p<0.05, **p<0,005 indicate significantly different from baseline



Changes in VAS score at Day 90 from baseline. VAS scores from each treatment group were compared to baseline value at specified time points. Each bar presents mean +/- SEM. **p<0,05 indicates significantly different from baseline

UC-II has been also evaluated in dogs using objective and semi-objective endpoints. Studies very consistently confirm the great interest of UC-II previously depicted in human and horses.

*Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial - David C. Crowley et al. International Journal of Medical Science, 6(6):312-321, 2009

UC-II in dogs, efficacy assesment by semi-objective data

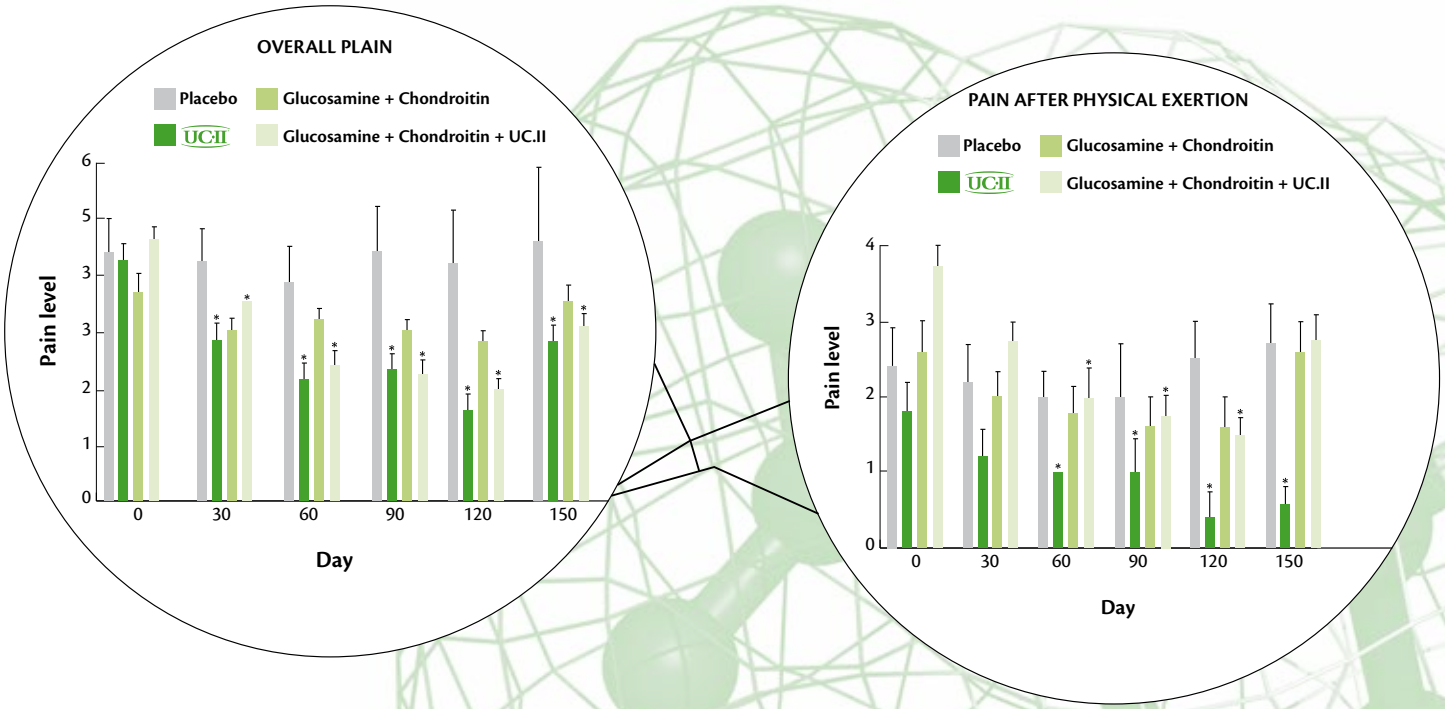
***Therapeutic efficacy and safety of undenatured type II collagen singly or in combination with Glucosamine and Chondroitin in arthritic dogs* - M. D'Altilio et al. Toxicology Mechanimsms and methods, 17:1-8,2007**

Main protocol features:

- Performed at Murray State University (KY, USA)
- 20 client owned dogs with clinical signs of osteoarthritis
- Randomly divided into 4 groups:
  - *Group I: Placebo*
  - *Group II: 40 mg providing 10 mg of active UC-II once a day*
  - *Group III: 2g Glucosamine + 1,6 g Chondroïn*
  - *Group IV: UCII + Glucosamine + Chondroitin*
- Treated once a day for 120 days followed by 30 days withdrawal
- No NSAID treatement 3 weeks before and during the course of the study
- Double blinded (investigators and owners)
- Clinical endpoints: overall pain (by pet owner), pain upon manipulation, exercise associated lameness.

Results and Conclusions

- Excellent tolerance in every group: no adverse effect, no change in hepatic or renal blood parameters
- No change in Placebo group.
- Only owners of dogs receiving UC-II (Groups II and IV) reported an overall improvement from first evaluation (30d)(consistent with results from Peal et al. J Vet Pharmacol Ther 2007)
- Limb manipulation and lameness at exercise were significantly improved in Groups II and IV from day 60.



UC-II in dogs, efficacy assesment by objective data

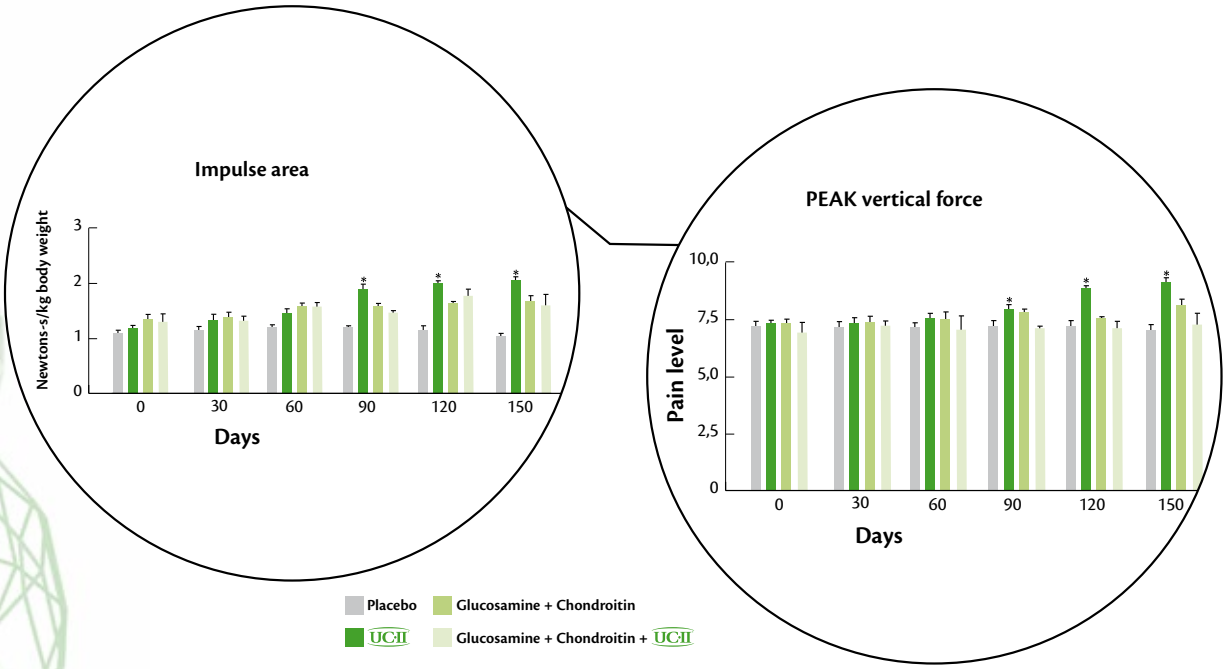
Comparative therpaeutic efficacy and safety of type II collagen (UC-II), glucosamine and chondrotin in arthritic dogs: pain evaluation by ground force plate – R.C. Gupta et al., J Anim Physiol Anim Nutrition, 96:770-777,2012

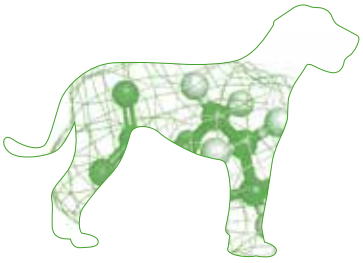
Main protocol features:

- Performed at Murray State University (KY, USA)
- Client owned dogs with clinical signs of moderate osteoarthritis
- Dogs weighing over 40 pounds (18.1kg), without severe concurrent disease
- Randomly divided into 4 groups (n=7-10 dogs/group):
  - *Group I: Placebo*
  - *Group II: 40 mg providing 10 mg of active UC-II once a day*
  - *Group III: 2g Glucosamine + 1,6 g Chondroïn*
  - *Group IV: UC-II + Glucosamine + Chondroitin*
- Treated once a day for 150 days
- No NSAID treatement 3 weeks before and during the course of the study
- Double blinded (investigators and owners)
- Clinical endpoints: overall pain (owner questionnaire), pain upon manipulation, exercise associated lameness.
- Objective evaluation by Ground Force Plate.

Results and Conclusions

- Excellent tolerance in every group: no adverse effects, no change in hepatic or renal blood parameters
- No change in the placebo group
- Clinical signs (including overall pain assessed by pet owner) were significantly improved from day 60 in Group II.
- GFP parameters exhibited a constant improvement, with significance reached from day 90.





Publications about UC-II

Comparative therapeutic efficacy and safety of type-II collagen (UC-II), glucosamine and chondroitin in arthritic dogs: pain evaluation by ground force plate. Gupta RC, Canerdy TD, Lindley J, Konemann M, Minniear J, Carroll BA, Hendrick C, Goad JT, Rohde K, Doss R, Bagchi M, Bagchi D. J Anim Physiol Anim Nutr (Berl). 2012 Oct;96(5):770-7.

Nutritional interventions to prevent and treat osteoarthritis. Part II: focus on micronutrients and supportive nutraceuticals. Lopez HL. PM R. 2012 May;4(5 Suppl):S155-68.

Therapeutic efficacy of undenatured type-II collagen (UC-II) in comparison to glucosamine and chondroitin in arthritic horses. Gupta RC, Canerdy TD, Skaggs P, Stocker A, Zyrkowski G, Burke R, Wegford K, Goad JT, Rohde K, Barnett D, DeWees W, Bagchi M, Bagchi D. J Vet Pharmacol Ther. 2009 Dec;32(6):577-84.

Safety and toxicological evaluation of undenatured type II collagen. Marone PA, Lau FC, Gupta RC, Bagchi M, Bagchi D. Toxicol Mech Methods. 2010 May;20(4):175-89.

Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial. Crowley DC, Lau FC, Sharma P, Evans M, Guthrie N, Bagchi M, Bagchi D, Dey DK, Raychaudhuri SP. Int J Med Sci. 2009 Oct 9;6(6):312-21.

Therapeutic efficacy and safety of undenatured type-II collagen (UC-II) alone or in combination with (-)-hydroxycitric acid and chromemate in arthritic dogs. Peal A, D'Altilio M, Simms C, Alvey M, Gupta RC, Goad JT, Canerdy TD, Bagchi M, Bagchi D. J Vet Pharmacol Ther. 2007 Jun;30(3):275-8.

Therapeutic Efficacy and Safety of Undenatured Type II Collagen Singly or in Combination with Glucosamine and Chondroitin in Arthritic Dogs. D'Altilio M, Peal A, Alvey M, Simms C, Curtsinger A, Gupta RC, Canerdy TD, Goad JT, Bagchi M, Bagchi D. Toxicol Mech Methods. 2007;17(4):189-96.

Efficacy and safety of glycosylated undenatured type-II collagen (UC-II) in therapy of arthritic dogs. Deparle LA, Gupta RC, Canerdy TD, Goad JT, D'Altilio M, Bagchi M, Bagchi D. J Vet Pharmacol Ther. 2005 Aug;28(4):385-90.

Effects of orally administered undenatured type II collagen against arthritic inflammatory diseases: a mechanistic exploration. Bagchi D, Misner B, Bagchi M, Kothari SC, Downs BW, Fafard RD, Preuss HG. Int J Clin Pharmacol Res. 2002;22(3-4):101-10.