UC-II® Undenatured Type II Collagen for Joint Health

Executive Summary

Several clinical trials have demonstrated that **UC-II®** undenatured type II collagen offers joint health benefits not only for people with osteoarthritis (OA), but for healthy adults. In 2002, Bagchi et al[1] successfully showed that women with joint-health problems were able to achieve clinically meaningful joint-health benefits with **UC-II®** undenatured type II collagen after 42 days in a small pilot study with no placebo. Subsequently, two clinical trials (Crowley et al[2] and Lugo et al[3]) confirmed similar benefits in people with knee OA. In these controlled trials, **UC-II®** undenatured type II collagen was statistically significantly more effective than glucosamine + chondroitin as measured by WOMAC. In a third randomized placebo-controlled clinical trial (Lugo et al[4]), **UC-II®** undenatured type II collagen was found to significantly improve post-exercise recovery, when compared to baseline, in healthy adults who experience joint pain after climbing steps. Overall, **UC-II®** undenatured type II collagen was well tolerated with an effective daily dose of 40 mg.

Animal studies have demonstrated similar joint health benefits in companion dogs and horses. Results from studies with companion dogs[5,6] and one study with horses[7] indicate significant joint-health benefits with **UC-II®** undenatured type II collagen alone compared to placebo or to glucosamine + chondroitin supplementation. The effective amounts of **UC-II®** undenatured type II collagen (40 mg/day for dogs; 480 mg/day for horses) were well tolerated with study durations ranging from 3 to 5 months. In a rat model of OA (Bagi et al[8]), **UC-II®** undenatured type II collagen significantly improved post-surgical knee structure and function and preserved knee cartilage with an amount equivalent to the clinically effective dose (40 mg/day) for humans.

The ability of UC-II® undenatured type II collagen to support joint comfort, mobility and flexibility is attributed to its undenatured type II collagen. In 2002, Bagchi et al1 showed that UC-II® undenatured type II collagen contains biologically active epitopes that are believed to be responsible for the UC-II® undenatured type II collagen proposed mechanism of action and its potential role in oral tolerization. At the level of the Peyer's patches in the gut, UC-II® undenatured type II collagen interacts with dendritic cells to stimulate the immune T regulators (Treg). Treg produce the IL-10 cytokine and the transforming growth factor b (TGFb) which stimulate the chondrocytes to produce type II collagen.

UC-II® undenatured type II collagen has a broad-spectrum safety profile based on numerous toxicology assessments (Marone et al[9]). Results indicate that **UC-II®** undenatured type II collagen has an acute oral LD_{50} greater than 5,000 mg/kg and an acute dermal LD_{50} greater than 2,000 mg/kg. It is non-mutagenic, non-

Key Definitions

UC-II® Undenatured Type II Collagen – Brand name for the patented form of collagen powder with undenatured (native) type II collagen, the active form important for optimal joint health support.

Osteoarthritis (OA) – According to the Arthritis Foundation, OA is the most common form of arthritis, affecting more than 30 million Americans. Aging is a major risk factor, but anyone who injures or overuses their joints, including athletes, military members, and people who work physically demanding jobs, may be more susceptible to developing OA as they age.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) – A clinically validated questionnaire used to assess arthritis symptoms in three domains (subscales): physical function, stiffness and knee pain.

genotoxic, slightly irritating to the skin, and moderately irritating to the eye. In addition, the no-observed-adverse-effect level (NOAEL) for **UC-II®** undenatured type II collagen is reported to be 400 mg/kg/day, which is substantially higher than the clinically effective dose (40 mg/day or 0.57 mg/kg/day for a 70 kg man). The Burdock Group, an independent, leading science and regulatory consulting firm, has completed a critical evaluation of safety data,[10] concluding that **UC-II®** undenatured type II collagen is safe for human consumption and affirming its status as a generally recognized as safe (GRAS) food ingredient.

Human Research

UC-II® undenatured type II collagen improves post-exercise knee extension and comfort in healthy adults.

At a Glance	
Publication	Lugo et al. *J Int Soc Sports Nutr.* 2013;10(1):48.
Study Design	R, DB, PC
Participants	• 106 adults screened; 55 adults enrolled; 46 completers • Mean age: 46 years • Otherwise healthy with post-exercise joint pain
Duration	120 days
Intervention	40 mg/day UC-II®
Control	Placebo
Key Findings	UC-II® is well tolerated and offers clinically meaningful benefits for healthy adults who experience transient joint pain after strenuous exercise.

R, randomized; DB, double-blind; PC, placebo-controlled.

In this randomized, double-blind, placebo-controlled study,4 Lugo and colleagues demonstrated the efficacy and tolerability of **UC-II®** undenatured type II collagen joint-health benefits in healthy, active adults. Participants included adults without knee joint pain at rest, without arthritic disease based on the American College of Rheumatology guidelines, and with no active use of medications or dietary supplements that would impact joint comfort.

A total of 55 participants (23 men, 32 women), mean age 46 years, who met the inclusion criteria, were enrolled and randomly assigned to one of two daily supplements for 120 days: **UC-II®** undenatured type II collagen (40 mg) or placebo. As a primary endpoint, joint function was assessed by the range of motion (ROM) which reflects changes in degree of knee flexion and knee extension. As secondary endpoints, the length of time to experience and recover from joint pain following strenuous stepmill exertion were measured.

Completers included 89% (24/27) of participants in the **UC-II®** group and 79% (22/28) in the placebo group. (Two participants in the placebo group did not participate in the range of motion assessment.) No product related adverse events were observed during the study.
Results indicate that, compared to placebo, **UC-II®** undenatured type II collagen significantly (*P*=.01) improved average knee extension by almost 10% (74.0 ± 2.2º vs. 81.0 ± 1.3º, respectively) among completers. Compared to placebo, average knee extension significantly improved at Day 120 (81.0 ± 1.3º vs. 73.2 ± 1.9º; *P*=.002) and as early as Day 90 from baseline (78.8 ± 1.9º vs. 73.2 ± 1.9º; *P*=.045). No significant change in knee extension was observed in the placebo group at any time. Compared to baseline, **UC-II®** supplementation doubled the average exercise time before any joint discomfort at Day 120 (1.4 ± 0.2 min vs. 2.8 ± 0.5 min, *P*<.02). No significant changes in any parameter measured were found in the placebo group. Interestingly, five participants taking **UC-II®** undenatured type II collagen reported no pain during or after the stepmill protocol (*P*=.03, within visit) compared to one participant in the placebo group.

These findings indicate that **UC-II®** undenatured type II collagen (40 mg/day for 4 months) is well tolerated and offers clinically meaningful improvements in post-exercise knee extension and comfort in healthy adults.

UC-II® undenatured type II collagen is more effective than placebo and glucosamine + chondroitin in adults.

At a Glance	
Publication	Lugo et al. *Nutr J.* 2016;15:14.
Study Design	• MC (n=13), R, DB, PC
Participants	• 234 adults screened; 191 enrolled; 164 completers • Mean age: 53 years • Diagnosed with OA
Duration	180 days
Intervention	40 mg/day UC-II® 1,500 mg G + 1,200 mg C/day
Control	Placebo
Key Findings	UC-II® is well-tolerated and superior to GC for providing clinically meaningful benefits for joint comfort, flexibility and physical function.

MC, multi-center; R, randomized; DB, double-blind; PC, placebo-controlled; OA, osteoarthritis; G, glucosamine hydrochloride; C, chondroitin sulfate.

In this multi-center (n=13), randomized, double-blind, placebo-controlled study,[3] the efficacy of **UC-II®** supplementation was compared to glucosamine + chondroitin (GC).

A total of 191 middle-aged men and women with clinically validated moderate-to-severe OA were enrolled and randomly assigned to one of three daily supplements for 180 days: **UC-II®** undenatured type II collagen (40 mg), GC (1,500 mg G & 1,200 mg C) or placebo. The primary endpoint was the change in total WOMAC score. Secondary endpoints included the Lequesne Functional Index (LFI), Visual Analog Scale (VAS) for pain, and WOMAC subscales.

A total of 164 subjects (164/191; 86%) completed the study; dropouts were due to reasons other than study product use. Among completers, **UC-II®** undenatured type II collagen significantly ($P<.05$) reduced the total WOMAC score compared to placebo and GC as measured by analysis of covariance (ANCOVA) at the end of the study. A stratified analysis of cartilage oligomeric matrix protein (COMP) — a serum biomarker of joint damage — showed that, among participants with higher baseline levels ($\geq$285 mg/mL), those in the **UC-II®** group had significantly ($P<.05$) greater reductions in the total WOMAC score for subjects stratified based on baseline COMP levels than those in either the placebo or GC group at the end of the study.

UC-II® undenatured type II collagen significantly reduced WOMAC subscales and mean VAS and LFI function scores at Day 180 compared to either placebo or GC. No significant changes were observed between the GC and placebo groups for any functional score measured. Although safety outcomes were similar among the groups, the use of rescue medication was lower in the **UC-II®** group than in the GC or placebo groups.

UC-II® undenatured type II collagen (40 mg/day for 6 months) is well-tolerated and significantly more effective than GC for supporting joint health in adults with knee OA.

UC-II® undenatured type II collagen is more effective than glucosamine + chondroitin in adults in a pilot study

At a Glance	
Publication	Crowley et al. *Int J Med Sci.* 2009;6(6):312-21.
Study Design	MC (n=2), R, DB, Comparison
Participants	• 52 adults enrolled • Mean age: 59 years • Diagnosed with moderate knee OA
Duration	90 days
Intervention	40 mg/day UC-II® or 1,500 mg G + 1,200 mg C/day
Control	None
Key Findings	UC-II® is well-tolerated and more effective than GC in key areas of joint health.

MC, multi-center; R, randomized; DB, double-blind; PC, placebo-controlled; OA, osteoarthritis; G, glucosamine hydrochloride; C, chondroitin sulfate.

In this pilot study,2 Crowley and colleagues showed the efficacy of **UC-II®** undenatured type II collagen for joint-health support in people with OA compared to glucosamine + chondroitin (GC).

A total of 52 adults, mean age 59 years, with clinically validated moderate knee OA were randomly assigned to one of two daily supplements for 90 days: **UC-II®** undenatured type II collagen (40 mg) or GC (1,500 mg G and 1,200 mg C). Clinical assessments were done at

baseline, 30, 60 and 90 days, including scores for total WOMAC, Lequesne Functional Index (LFI), and Visual Analog Scale (VAS). Participants completed a diary throughout the study to monitor side effects, medication use and compliance.

No significant between-group difference in adverse effects was reported. More participants needed rescue medications with GC than with **UC-II®** supplementation at all time points.

After 90 days, **UC-II®** supplementation reduced the WOMAC score more than GC (33% vs. 14%, respectively), reduced significantly the VAS score more than GC (40% vs. 15%, respectively), and reduced the LFI function score more than GC (20% vs. 6% respectively). Unlike the improvements with GC, all improvements with **UC-II®** supplementation in these functional parameters reached statistical significance (*P*<.05).

UC-II® undenatured type II collagen (40 mg/day for 90 days) is well tolerated and more effective than GC as measured by WOMAC in people with moderate-to-severe knee OA.

UC-II® undenatured type II collagen supports joint health and contains biologically active epitopes with the ability to induce oral tolerization.

At a Glance	
Publication	Bagchi et al. *Int J Clin Pharmacol Res.* 2002;22(3-4):101-10.
Study Design	• OL pilot study • ELISA assay and EMA
Participants	• 5 women, aged 58-78 years • Diagnosed with OA or reporting similar symptoms
Duration	42 days
Intervention	40 mg/day UC-II®
Control	None
Key Findings	• UC-II® is well-tolerated with joint-health benefits reported as early as 3 weeks. • Active epitopes identified in UC-II® undenatured type II collagen.

OL, open-label; ELISA, enzyme-linked immunosorbent assay; EMA, electron microscopy analysis; OA, osteoarthritis.

In an open-label, pilot study,1 Bagchi and colleagues demonstrated the efficacy and tolerability of **UC-II®** undenatured type II collagen for joint-health benefits. In separate laboratory analyses, the researchers confirmed the presence of biologically active epitopes required for oral tolerization, the mechanism by which **UC-II®** undenatured type II collagen is believed to work.

For the pilot study, the researchers enrolled five women, aged 58 to 78 years, with significant joint discomfort, two of whom had been clinically diagnosed with OA. The women were asked to take a single daily dose of **UC-II®** undenatured type II collagen (40 mg) for 42 days and record their respective discomfort levels using a hedonic scale (1=tolerable to 10=unbearable) at baseline and once every 7 days.

After 42 days, all but one participant reported joint-health benefits as early as the third week of supplementation from the beginning of the trial. In the four responders, **UC-II®** undenatured type II collagen was associated with an overall mean 26% reduction in perceived discomfort from baseline. No side effects were associated with **UC-II®** undenatured type II collagen

Results from a validated enzyme-linked immunosorbent assay (ELISA) showed that **UC-II®** undenatured type II collagen contains glycosylated biologically active epitopes with the correct composition and structural conformity of galactose-dependent glycoprotein. Further, electron microscopy analysis showed that the epitopes are a triple helix structure that is partially preserved in gastric juice. After incubation in simulated gastric juice for 90 minutes, about 50% of the soluble **UC-II®** undenatured type II collagen remained in the biologically active epitope form.

The researchers propose **UC-II®** undenatured type II collagen works via these epitopes as they survive digestion with the three-dimensional structure needed to interact with the lymphoid tissue surrounding the small intestine (Peyer's patches). In this way, **UC-II®** undenatured type II collagen is believed to affect the gut immune system by oral tolerization to turn off the immune

response targeting type II collagen in joint cartilage.

Supporting Research

UC-II® undenatured type II collagen improves post-injury function and supports healthy knee cartilage in rat model of osteoarthritis.

Using a rat model of OA,[8] Bagi and colleagues demonstrated the ability of **UC-II®** undenatured type II collagen accelerated articular cartilage structure in an intervention study.

For this study, the researchers performed partial medial meniscectomy tear (PMMT) surgery in 20 male rats to induce OA. For 8 weeks, beginning immediately with the surgery, 10 rats received an oral dose of **UC-II®** undenatured type II collagen (0.66 mg/kg/day), equivalent to a clinically effective dose of 40 mg/day in humans, while another 10 rats received vehicle only (0.5% methyl cellulose). Separately, 10 naïve rats served as intact controls and another 10 rats received sham surgery. Dynamic weight-bearing capacity of front and hind legs, serum biomarkers of bone and cartilage metabolism, integrity of subchondral and cancellous bone at the tibial epiphysis and metaphysis using imaging, and cartilage pathology using histochemistry staining at the medial tibial plateau were assessed.

The PMMT surgery produced moderate OA at the medial tibial plateau and deterioration of articular cartilage, which reduced the weight-bearing capacity of the operated limb. However, **UC-II®** undenatured type II collagen, beginning immediately after surgery, not only preserved the weight-bearing capacity of the injured leg, but preserved the integrity of the cancellous bone at the tibial metaphysis and limited excessive osteophyte formation and deterioration of articular cartilage.

These preliminary findings suggest that taking a clinically relevant daily dose of **UC-II®** undenatured type II collagen, starting immediately after knee injury, can support mechanical function and help maintain joint cartilage and bone integrity of the injured knee joint.

Companion Animal Research

UC-II® undenatured type II collagen is well tolerated and more effective than glucosamine + chondroitin for arthritis-related discomfort in horses.

In this animal study,[7] Gupta and colleagues demonstrated the efficacy of the oral intake of **UC-II®** undenatured type II collagen compared to glucosamine + chondroitin (GC) for joint health in horses with clinically diagnosed, moderately severe OA.

For this study, researchers selected horses from the Murray State University Equine Center based on outward visual signs of lameness. Five groups of horses (5-6 horses per group) were given various daily supplements for 5 months: placebo, **UC-II®** undenatured type II collagen (320, 480, or 640 mg), or GC (5.4 and 1.8 g, respectively, twice daily for the first month and once daily thereafter).

The horses were evaluated for overall discomfort, discomfort upon limb manipulation, physical examination, and liver and kidney functions. Horses receiving placebo showed no change, while those receiving all dosages of **UC-II®** undenatured type II collagen exhibited significant reductions in discomfort ($P<.05$). The higher daily doses of **UC-II®** undenatured type II collagen (480 mg and 640 mg) provided equal benefits, indicating 480 mg/day was optimal. At this dose, overall discomfort reduced from 100% to 12% and discomfort upon limb manipulation reduced from 100% to 22%. Although the GC group showed a significant ($P<.05$) reduction in discomfort compared to baseline, efficacy was less than that with **UC-II®** undenatured type II collagen. No changes in the clinical condition (i.e., body weight, body temperature, respiration rate and pulse rate) or liver and kidney functions were reported.

UC-II® undenatured type II collagen alone is well tolerated and more effective than glucosamine + chondroitin for joint health benefits in objective quantitative assessment research

In this animal study,5 Gupta and colleagues showed that **UC-II®** undenatured type II collagen was efficacious in supporting joint-health in client-owned, moderately arthritic, companion dogs.

For this study, researchers followed four groups of adult dogs, each weighing over 40 lbs, with 7 to 10 dogs per group, that were given one of four daily supplements for 5 months: placebo, **UC-II®** undenatured type II collagen (40 mg), GC (2.0 g and 1.6 g, respectively), or **UC-II®** undenatured type II collagen and GC combined. Both researchers and owners were blinded to the randomization, and all dogs remained with their owners throughout the study. On a monthly basis, discomfort was evaluated in each dog by observation (i.e., overall discomfort, discomfort upon limb manipulation, and discomfort after physical exertion) and measured quantitatively by ground force plate (GFP) parameters (i.e., peak vertical force and impulse area). Dogs were also examined every month for physical condition as well as liver and kidney functions.

While discomfort as measured by observation significantly ($P<.05$) reduced in all active groups, only the **UC-II®** group experienced a significant increase in the quantitative GFP-based parameters (as early as Day 90), which is indicative of a significant reduction in discomfort associated with arthritis. None of the dogs in any group showed changes in physical condition or liver and kidney functions.

These findings indicate **UC-II®** supplementation alone (40 mg/day for 5 months) is well tolerated and significantly increases comfort in moderately arthritic dogs.

The researchers also noted that these findings suggest different mechanisms of action are at work. Glucosamine may help enhance proteoglycan synthesis, which is impaired in OA cartilage. Chondroitin helps keep cartilage tissue hydrated, elastic and resilient to impact stress. By contrast, a small amount of **UC-II®** undenatured type II collagen, taken orally, is believed to work by oral tolerance. That is, **UC-II®** undenatured type II collagen may improve joint mobility, flexibility and comfort by preventing the immune system from attacking and damaging its own joint cartilage.

UC II® undenatured type II collagen is well tolerated and provides significant joint health benefits in companion dogs.

In this animal study,6 D'Altilio and colleagues demonstrated the efficacy, tolerability and safety of the oral intake of **UC-II®** undenatured type II collagen and glucosamine + chondroitin (GC) for increased comfort in moderately arthritic, companion dogs.

For this study, researchers followed companion dogs that were given a placebo, **UC-II®** undenatured type II collagen (40 mg) or GC (2.0 g and 1.6 g, respectively), or **UC-II®** undenatured type II collagen for 4 months. Both researchers and owners were blinded to the randomization. On a monthly basis, discomfort was evaluated in each dog by observation (i.e., overall discomfort, discomfort upon limb manipulation, and discomfort after physical exertion). Dogs were examined every month for body weight as well as liver and kidney functions.

Dogs receiving **UC-II®** undenatured type II collagen alone showed a significant reduction in overall discomfort within 30 days (33%) and discomfort upon limb manipulation and exercise-associated lameness after 60 days (66% and 44%, respectively) of supplementation. Maximum reductions in discomfort were noted after 120 days of supplementation (overall discomfort, 62%; discomfort upon limb manipulation, 91%; and exercise-associated lameness, 78%). In addition, dogs supplemented with **UC-II®** undenatured type II collagen were more playful and energetic compared to other groups. By contrast, GC alone

alleviated some discomfort but not significantly (*P*>.05). No adverse effects were reported.

These findings indicate that **UC-II®** undenatured type II collagen (40 mg/day for 4 months) is well tolerated and provides significant joint-health benefits in companion dogs.

Safety Research

UC-II® undenatured type II collagen exhibits a broad-spectrum safety profile based on extensive toxicology testing.

In 2010, Marone and colleagues performed an extensive toxicology study[9] of **UC-II®** undenatured type II collagen, including oral and dermal toxicity, skin and eye irritation, genotoxicity and mutagenicity assessments.

Results indicate that **UC-II®** undenatured type II collagen has an acute oral LD_{50} greater than 5,000 mg/kg and an acute dermal LD_{50} greater than 2,000 mg/kg. **UC-II®** undenatured type II collagen was classified as slightly irritating to the skin and moderately irritating to the eye, based on primary skin and eye irritation tests.

UC-II® undenatured type II collagen was found to be non-mutagenic as measured by the Ames bacterial reverse mutation test in five *Salmonella typhimurium* strains either with or without metabolic activation (S9). **UC-II®** undenatured type II collagen was also found to be non-genotoxic as measured by another gene mutation test, the mouse lymphoma cells either with or without metabolic activation.

Finally, results from a dose-dependent, 90-day subchronic toxicity test in Sprague-Dawley rats found the no-observed-adverse-effect level (NOAEL) for the oral intake of **UC-II®** undenatured type II collagen to be 400 mg/kg/day, which is substantially more than the clinically effective dose (40 mg/day or 0.57 mg/kg/day for a 70 kg man). Together, these findings demonstrate that **UC-II®** undenatured type II collagen exhibits a broad-spectrum safety profile.

Burdock Group confirms the broad-spectrum safety profile of UC-II® undenatured type II collagen and affirms GRAS status.

In 2009, the Burdock Group, a leading consultancy group, independently reviewed the safety research for **UC-II®** undenatured type II collagen in a thorough and critical evaluation.[10] The expert panel of toxicologists concluded that **UC-II®** undenatured type II collagen is safe for human consumption and affirmed its status as a generally recognized as safe (GRAS) food ingredient. **UC-II®** undenatured type II collagen is an FDA notified and registered new dietary ingredient (NDI).

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