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Clinical prospects of undenatured type II collagen: A novel approach in osteoarthritis management

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Abstract
Osteoarthritis is a debilitating joint disease characterized by progressive cartilage breakdown and limited treatment options. Undenatured type II collagen has gained significant attention as a nutraceutical that harnesses the body's immune system through oral tolerance. By interacting with gut-associated lymphoid tissue, undenatured type II collagen stimulates regulatory T cells that effectively suppress joint inflammation and promote cartilage repair. Extensive preclinical studies across multiple species including bovine, porcine, squid, chicken, and Nile tilapia demonstrate Undenatured type II collagen's consistent ability to reduce key inflammatory mediators (IL-1β, TNF-α), inhibit cartilage-degrading enzymes (MMP-13), reducing cartilage degradation markers (CTX-II, COMP), and preserve joint structure. Clinical investigations reveal promising improvements in pain, joint function, and cartilage thickness in osteoarthritis patients treated with undenatured type II collagen. Despite these encouraging results, clinical evidence is still preliminary, highlighting the urgent need for large, randomized, placebo-controlled trials to establish undenatured type II collagen role in promoting cartilage health. This review underscores undenatured type II collagen's potential to reduce cartilage degradation and to promote cartilage repair in OA.

Keywords: Undenatured Type II collagen, cartilage degradation, cartilage repair, osteoarthritis, joint health

Introduction

Cartilage: Biochemical Composition and Normal Physiology

Articular cartilage is a specialized connective tissue found at the ends of bones within synovial joints, playing a crucial role in joint mobility and load distribution. It is primarily composed of water (70-80%), type II collagen, proteoglycans, and chondrocytes, with its unique structure enabling it to resist mechanical forces. The water content helps provide compressive resilience and contributes to the diffusion of nutrients, given the lack of blood vessels in cartilage [1]. Collagen, particularly type II collagen, is the main structural component of the cartilage extracellular matrix (ECM). Type II collagen forms a network of fibrils that provide tensile strength and maintain cartilage integrity. Proteoglycans, with aggrecan being the most abundant, bind to water molecules and offer compressive stiffness to cartilage [2]. This water-binding capacity is crucial for cartilage's function in joint mobility, enabling it to resist compressive loads during movement [1, 2]. Chondrocytes are the primary cells in cartilage, responsible for synthesizing and maintaining the ECM [3, 4]. They are embedded in lacunae and are exposed to a hypoxic environment, which is further modulated by mechanical stimuli. These cells are regulated by growth factors, including insulin-like growth factor 1 (IGF-1) and transforming growth factor-beta (TGF-β), which maintain the delicate balance between cartilage matrix synthesis and degradation [3, 4].

Cartilage Degradation in Osteoarthritis

Osteoarthritis (OA) is a degenerative joint disease that leads to progressive cartilage breakdown, along with subchondral bone remodeling, synovial inflammation, and osteophyte formation. It is influenced by multiple factors, including mechanical stress, genetic predisposition, and inflammatory mediators.

A significant characteristic of OA is the degradation of the cartilage ECM, particularly the loss of proteoglycans and collagen fibers, which impair the tissue's structural integrity and its ability to resist stress [5], [6]. The initial event in OA is often the degradation of aggrecan by aggrecanases, leading to a reduction in cartilage's water-binding capacity, which diminishes its compressive strength [7].

Subsequently, the collagen network, particularly type II collagen, undergoes degradation by matrix metalloproteinases (MMPs), such as MMP-13, which are upregulated during OA progression [8]. In addition to mechanical degradation, OA is marked by the upregulation of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), which enhance the expression of MMPs and inhibit ECM synthesis [9, 10]. This inflammatory environment accelerates cartilage loss and contributes to chondrocyte apoptosis. The subchondral bone also undergoes changes, including increased bone turnover and sclerosis, which alter joint biomechanics and exacerbate pain [9, 10].

Cartilage Health Monitoring: From Research to Clinics

Monitoring cartilage health is vital for diagnosing osteoarthritis early and assessing disease progression. Various imaging and biochemical techniques have been developed to evaluate cartilage integrity and predict OA outcomes.

Imaging Modalities

- **Magnetic Resonance Imaging (MRI):** MRI is the gold standard for visualizing cartilage integrity, allowing for the assessment of cartilage thickness, water content, and structural changes. Techniques like T2 mapping and T1ρ imaging can detect early OA-related alterations in cartilage composition, such as collagen damage and changes in proteoglycan content [11]. Moreover, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is used to assess glycosaminoglycan content, providing a sensitive measure of cartilage degradation [11].
- **Ultrasound:** High-resolution ultrasound is increasingly being used to measure cartilage thickness in joints such as the knee. It offers a non-invasive, real-time, and cost-effective tool for cartilage assessment. Studies have demonstrated that ultrasound measurements correlate well with MRI and histological data, making it a useful clinical tool for monitoring OA progression [12], [13].
- **Radiography:** Although X-ray imaging is limited in detecting early cartilage degradation, it remains an important tool for evaluating joint space narrowing and osteophyte formation in advanced OA [14].

Biochemical Markers

Biochemical markers that reflect cartilage metabolism have gained significant interest for their potential to detect early OA and monitor therapeutic interventions. Some prominent markers include:

- **Urinary C-terminal telopeptide of type II collagen:** This marker reflects the degradation of type II collagen and is highly specific to cartilage turnover. Elevated levels correlate with joint space narrowing and disease progression, making it an effective marker for OA [15], [16].
- **COMP (Cartilage Oligomeric Matrix Protein):** COMP is a pentameric protein found in cartilage and its levels are elevated in individuals with OA. Serum COMP concentrations correlate with cartilage loss and OA severity, and they have been shown to predict the need for joint replacement surgery [17].
- **C2C and C1, 2C:** These neoepitopes are generated by collagen type II cleavage and are detectable in synovial fluid and serum. Elevated levels of C2C and C1, 2C have been associated with early OA and cartilage degradation post-injury [18].

The combination of these markers with imaging techniques provides a powerful approach for assessing cartilage health and guiding OA management.

Given the multifactorial nature of OA and the central role of articular cartilage degradation in its pathogenesis, preserving cartilage integrity has become a key therapeutic goal [19], [20]. Despite advances in diagnostic tools and symptomatic management, there is currently no curative treatment for OA, and approved disease-modifying osteoarthritis drugs (DMOADs) remain elusive [21]. Among emerging nutraceutical interventions, Undenatured type II collagen (uDIIC) has gained significant attention for its immunomodulatory potential and ability to promote joint health by inducing oral tolerance to endogenous type II collagen thereby reducing T-cell mediated inflammation and subsequent cartilage degradation [22, 23]. Unlike hydrolyzed collagen or glucosamine-based supplements, uDIIC retains its native triple-helical structure, which is essential for its interaction with gut-associated lymphoid tissue (GALT) in Peyer's patch and for the generation of regulatory T (Treg) cells that suppress inflammatory responses in joints [22, 23]. Recent randomized clinical trials and preclinical studies support uDIIC's capacity to improve joint comfort, flexibility, and reduce cartilage catabolism in both human and animal OA models [24-27]. This review will focus on the evidence supporting the use of uDIIC as a promising nutraceutical strategy to maintain articular cartilage integrity and potentially slow the progression of OA.

Materials and Methods

This review sought to systematically and comprehensively evaluate the role of uDIIC in maintaining and supporting articular cartilage health, with a particular focus on its influence on cartilage metabolism, degradation, and repair processes. A structured literature search was conducted across PubMed, Google Scholar, ScienceDirect, and ClinicalTrials.gov from database inception through March 2025, without language restrictions. The search strategy incorporated both Medical Subject Headings (MeSH) and free-text terms, including: ("undenatured type II collagen" or "native type II collagen" or "soluble undenatured type II collagen" or "insoluble undenatured type II collagen" or "naïve type II collagen" or "chicken type II collagen" or "type II collagen") and ("cartilage" or "cartilage degradation" or "cartilage damage" or "cartilage deterioration" or "cartilage repair" or "cartilage metabolism" or "C-Terminal Cross-Linked Telopeptides of Type II Collagen" OR "CTX-II" OR "uCTX-II" OR "COMP" or "C2C" or "C1,2C" or "Cartilage*"). Inclusion criteria comprised clinical trials and in vivo animal studies investigating the effects of uDIIC on cartilage structural integrity, functional outcomes, and biochemical markers such as uCTX-II, COMP, C2C, and C1, 2C. Exclusion criteria encompassed reviews, editorials, and studies not directly assessing articular cartilage or those limited to hydrolyzed or denatured collagen formulations. Studies utilizing uDIIC in combination with other agents without an appropriate control arm isolating uDIIC's effects were also excluded. In instances of duplicate publications, the

most comprehensive version was retained for analysis.

Results

Role of undenatured type II collagen in maintaining cartilage health

Concept of immuno-modulation (oral tolerance)-mechanism of action

When undenatured type II collagen is ingested, it resists denaturation by gastric enzymes and remains intact through the upper gastrointestinal tract until it reaches the small intestine. Within small intestine, specialized lymphoid structures (GALT) known as Peyer's patches interact with it. These regions (Peyer's patch) contain dendritic cells and T cells, which play a crucial role in oral tolerance development of uDIIC. From mucus layer, uDIIC comes into contact with the intestinal epithelial lining, dendritic cells capture uDIIC by binding to specific regions in its structure called epitopes and transport it into Peyer's patches. There, they function as antigen-presenting cells (APCs), presenting uDIIC to naive T cells and form Major Histocompatibility Complex (MHC). This complex comprising uDIIC, dendritic cells, and T cells initiates the differentiation of T cells into Treg cells. These Treg cells enters the circulation and reaches to inflamed joint tissues. They modulate the inflammatory environment by increasing IL-10 production, an anti-inflammatory cytokine, decreasing levels of pro-inflammatory cytokines like IL-1β and IL-6, and promoting anabolic pathways by enhancing the production of Transforming Growth Factor-beta (TGF-β) and type II collagen. Through this process, uDIIC helps mitigate the autoimmune-driven cartilage degradation characteristic of joint disorders such as OA [28], [29].

Undenatured type II collagen in cartilage health-preclinical studies

This was explored the ability of orally administered soluble undenatured type II collagen (uDIIC), derived from fetal bovine articular cartilage and purified via limited pepsin digestion (with purity validated by amino acid analysis and SDS-PAGE through Genetic Design, Watertown, MA), to modulate cartilage-specific autoimmune responses in a murine model of collagen-induced arthritis (CIA) [30]. Mice fed 500 µg of uDIIC intragastrically for 12 doses over 6 weeks demonstrated a significant reduction in arthritis incidence (p<0.004 after day 30) and a lower maximum arthritic index (MAI) of 1.9 compared to 3.9 in controls by day 58. Importantly, denatured collagen (heat-treated at 56°C) failed to show any protective effect, highlighting the necessity of the intact triple-helical structure of native cartilage collagen for immune modulation. Despite comparable overall antibody titers, mice that received uDIIC showed a marked reduction in cartilage-reactive IgG2b antibodies (30±9 µg/mL vs. 107±17 µg/mL in controls; P=0.03), while IgG2a levels also trended downward. These IgG subclasses are directly implicated in cartilage destruction via complement activation and antibody-mediated inflammation [31]. The preservation of cartilage integrity in the treated group, despite immunization, supports the conclusion that oral administration of uDIIC selectively downregulates pathogenic immune responses targeting articular cartilage, offering a biologically specific strategy to protect cartilage from autoimmune-mediated degradation in arthritis [30].

The cartilage-protective effects of low-dose porcine uDIIC in a rat model of monoiodoacetate (MIA)-induced OA was evaluated where uDIIC was administered orally at 1, 3, or 10 mg/kg/day for 13 days, starting from the day of MIA injection. Biochemical analysis on day 14 revealed a 4-fold increase in plasma CTX-II, a validated biomarker of type II collagen degradation, in MIA + vehicle rats compared to controls. Treatment with uDIIC at 1 mg/kg reduced plasma CTX-II by 53%, and urinary CTX-II by 75%, indicating significant inhibition of cartilage breakdown. Notably, CPII (a marker of type II collagen synthesis) levels were not altered. These cartilage-specific findings underscore that oral administration of low-dose uDIIC effectively protects cartilage structure in OA by inhibiting its degradation [32].

In a study the cartilage-protective effects of chicken uDIIC derived from chicken sternum cartilage in a rat model of OA induced by partial medial meniscectomy tear (PMMT) was evaluated. uDIIC was administered orally at a clinically relevant dose of 0.66 mg/kg/day for 8 weeks, beginning immediately post-surgery. Histological analysis revealed that uDIIC significantly reduced the width of cartilage matrix loss and cartilage degeneration at the medial tibial plateau compared to vehicle-treated PMMT rats. Additionally, cartilage thickening and fibrillation in critical load-bearing zones were attenuated in uDIIC-treated rats, with smaller osteophyte formation and improved cartilage consolidation observed in Zones 1 and 3. Importantly, uDIIC also led to a significant reduction in CTX-II levels, supporting its role in preserving cartilage integrity. The study concludes that oral uDIIC, when initiated at the time of joint injury, mitigates cartilage damage and supports joint structure, indicating its potential as a disease-modifying intervention in OA [33].

In a study, the cartilage-protective potential of squid-derived type II collagen, isolated from Peru squid cartilage in a rat model of surgically induced OA [34]. Intra-articular administration of squid-derived type II collagen (3 mg/mL and 10 mg/mL, once weekly for 5 weeks) significantly preserved articular cartilage structure, as evidenced by gross morphology, HE staining, and Safranin O-Fast Green staining, which showed smoother cartilage surfaces and greater proteoglycan retention compared to untreated OA rats. Importantly, Osteoarthritis Research Society International (OARSI) scores used to quantify cartilage degeneration were significantly reduced in squid-derived type II collagen treated groups (p<0.01), indicating milder structural deterioration. Additionally, squid-derived type II collagen treated joints exhibited lower expression of MMP13 implicated in cartilage matrix breakdown and improved histological appearance of the cartilage matrix. These findings were further supported by decreased levels of inflammatory cytokines (TNF-α, IL-1β) in synovial fluid [34].

A study conducted a controlled clinical study to evaluate the chondroprotective efficacy of uDCII, derived from chicken sternum, in small-breed dogs diagnosed with OA secondary to medial patellar luxation (MPL) [35]. Dogs were administered a daily oral dose of 10 mg uDIIC for 16 weeks. Ultrasonographic evaluations revealed a statistically significant reduction in overall joint pathology, with the total ultrasonographic score decreasing from 5.846±1.345 at baseline (Day 0) to 3.692±1.251 at Week 16 (p<0.05). Synovial fluid scores also improved significantly, indicating reduced joint effusion and inflammation. However, cartilage-specific metrics showed limited structural improvement: the articular cartilage score at the proximal medial femoral condyle decreased modestly from 1.692±0.480 to 1.077±0.640, and cartilage thickness remained statistically unchanged across all measured regions (e.g., medial thickness at 0.196±0.059 mm at baseline vs. 0.196±0.043 mm at Week 16). Radiographic OA scores and lameness scores did not

show significant changes. These findings suggest that while uDIIC may exert beneficial anti-inflammatory effects and improve joint fluid characteristics, its direct regenerative impact on cartilage morphology and thickness in non-immune-mediated OA, such as that secondary to MPL, may be limited [35].

The therapeutic effects of uDIIC, extracted from chicken thoracic cartilage, on cartilage integrity and inflammation in a MIA induced OA rat model was investigated in a study [36]. Administered orally at doses of 4 mg/kg and 8 mg/kg daily for five weeks, uDIIC significantly improved cartilage-specific parameters. Histopathological analysis using the Mankin scoring system revealed that both low-and high-dose uDIIC groups exhibited markedly reduced cartilage degeneration compared to the model group, with articular cartilage scores improving from 5.12±0.83 in the model group to 3.62±0.92 and 3.50±0.81, respectively (p<0.05). Microscopically, uDIIC preserved cartilage architecture, reduced surface fissures, and maintained chondrocyte organization across the surface, transitional, radial, and calcified layers. Biochemically, uDIIC significantly decreased serum levels of cartilage degradation markers MMP-13 and CTX-II, with low-dose treatment reducing MMP-13 from 53.52±9.48 ng/mL to 43.12±8.96 ng/mL (p<0.01) and high-dose treatment lowering CTX-II from 5.27±1.32 ng/mL to 4.02±1.24 ng/mL (p<0.05). These findings underscore uDIIC's capacity to attenuate cartilage matrix breakdown and preserve structural integrity, likely through modulation of inflammatory cytokines and oxidative stress pathways, positioning it as a promising nutraceutical for OA cartilage preservation [36].

In a mechanistic study [37], OA was induced in rats via MIA, mimicking human OA features. Rats received uDIIC at a human-equivalent dose of 40 mg for 30 days. Post-treatment anti-inflammatory effects of uDIIC was observed as it significantly reduced systematic levels of key inflammatory markers, including TNF-α, IL-1β, IL-6, C-reactive protein (CRP), and Prostaglandin E2 (PGE2) (p<0.001). uDIIC also significantly decreased COMP (p<0.001), and increased osteocalcin, a marker associated with bone formation (p<0.0001). Improvements in oxidative stress markers, particularly Superoxide Dismutase (SOD) (p<0.05), were observed. Gait analysis demonstrated significant improvements in paw area, paw width, and stride length (p<0.01), and joint swelling was notably reduced. Radiographic and histological evaluations showed substantial reductions in Kellgren-Lawrence (KL) scores (p<0.05) and attenuation of cartilage damage, with decreased surface irregularity and matrix loss. Western blotting revealed significant reductions in Interferon Regulatory Factor-7 (IRF-7), Cyclooxygenase-2 (COX-2), NF-kB subunit IKK-gamma, Monocyte Chemoattractant Protein-1 (MCP-1), and MMP-3 levels (p<0.001) in articular joint. These findings substantiate uDIIC's role in reducing inflammatory pathways and cartilage degradation both at systemic as well as at articular joint level [37].

Another placebo-controlled study in healthy dogs was conducted [38], administering 40 mg of uDIIC over 13 weeks. The study out of many parameters also focused on COMP, a biomarker for cartilage metabolism and degradation. UDIIC treatment resulted in significant reductions in COMP levels across both sexes (P=0.003; P=0.01), with pronounced decreases following physical stress (16 km run) compared to placebo (P=0.023). These findings underscore uDIIC's potential in mitigating cartilage degradation induced by physical activity in higher animals as well.

A study evaluates the effects of uDIIC [39], sourced from chicken sternum on cartilage integrity in a rat model of MIA-induced OA. Administered orally at 4 mg/kg body weight for 30 days, uDIIC alone significantly mitigated cartilage degradation. Histopathological analysis using the Mankin scoring system showed a reduction in cartilage damage, with scores decreasing from 5.12±0.83 in the MIA group to 3.62±0.92 in the uDIIC-treated group (p<0.05). Western blot analysis of knee joint tissues revealed that uDIIC treatment restored type II collagen expression and significantly reduced the expression of cartilage-degrading and inflammatory markers, including MMP-3, NF-κB, and TGF-β1. Additionally, uDIIC lowered serum levels of COMP from 32.10±3.03 pg/mL in the MIA group to 25.76±2.98 pg/mL, and CRP from 10.76±1.45 pg/mL to 7.18±0.67 pg/mL. These biochemical and histological improvements were accompanied by functional recovery, as evidenced by increased stride length and reduced joint swelling. Collectively, these findings underscore uDIIC's capacity to preserve cartilage structure, suppress inflammatory mediators, and improve joint function in OA, supporting its role as a potent chondroprotective agent [39].

The cartilage-protective effects of undenatured type II collagen was examined in a study [40], sourced from chicken sternum in aging db/db mice, a model for diabetic OA degeneration. After 16 weeks of oral administration at 6 mg/kg, uDIIC significantly showed reduction in serum MMP-3, with levels in the uDIIC group (81.82±19.38 ng/L) significantly lower than those in the aging model (154.19±24.81 ng/L), young model (118.35±26.85 ng/L), and positive control (115.84±15.16 ng/L) groups (p<0.05). These data underscore uDIIC's efficacy in preserving cartilage microarchitecture and suppressing catabolic enzymatic activity, highlighting its potential as a therapeutic agent for cartilage degeneration in diabetic OA [40].

Investigation on the therapeutic efficacy of Nile tilapia-derived undenatured type II collagen was examined in a study [41], extracted from skull cartilage using a pepsin-solubilized method. The study demonstrated that oral administration of Nile tilapia-derived undenatured type II collagen at 3 mg/kg significantly enhanced cartilage repair in a rat model of arthritis, with histological analysis showing fully restored articular cartilage surfaces and organized chondrocyte layers, comparable to healthy controls. Quantitatively, IL-6 levels in $CD8^+$ T cells were reduced from 21.53 ng/L (control) to 5.56 ng/L at 50 µg/mL Nile tilapia-derived undenatured type II collagen (p<0.05), and IL-1β decreased from 11.71 ng/L to 4.24 ng/L at 1 µg/mL (p<0.05). Fas/Apo-1 expression peaked at 9.48 µg/L at 25 µg/mL Nile tilapia-derived undenatured type II collagen, and caspase-8 gene expression was significantly upregulated at 1-10 µg/mL (p<0.05), indicating apoptosis induction in $CD8^+$ T cells. These findings confirm that Nile tilapia-derived undenatured type II collagen promotes cartilage repair and immune tolerance by modulating inflammatory cytokines and apoptotic pathways [41]. A comparative efficacy of soluble and insoluble type II collagen was investigated [42] where both derived from chicken sternal cartilage, in mitigating OA in a MIA rat model. Both soluble and insoluble type II collagen were administered orally at a dose of 4.0 mg/kg/day (protein basis) for 28 days. Histopathological evaluation revealed that Soluble type II collagen significantly reduced cartilage degeneration, with the Mankin score decreasing from 9.50±0.84 in the model group to 6.00±2.10, and the OARSI

score from 5.83±0.41 to 3.00±1.26 (p<0.05). Insoluble type II collagen also showed improvement, with Mankin and OARSI scores of 6.17±2.14 and 3.33±1.63, respectively. Soluble type II collagen treated rats exhibited smoother cartilage surfaces and reduced exposure of subchondral bone, as confirmed by Safranin O-Fast Green staining. Furthermore, Soluble type II collagen significantly upregulated mRNA expression of anti-inflammatory markers IL-10, TGF-β, and Foxp3 in both spleen and intestinal tissues, and increased the proportion of $CD4^+CD25^+Foxp3^+$ regulatory T cells (Treg), indicating enhanced immune tolerance [42].

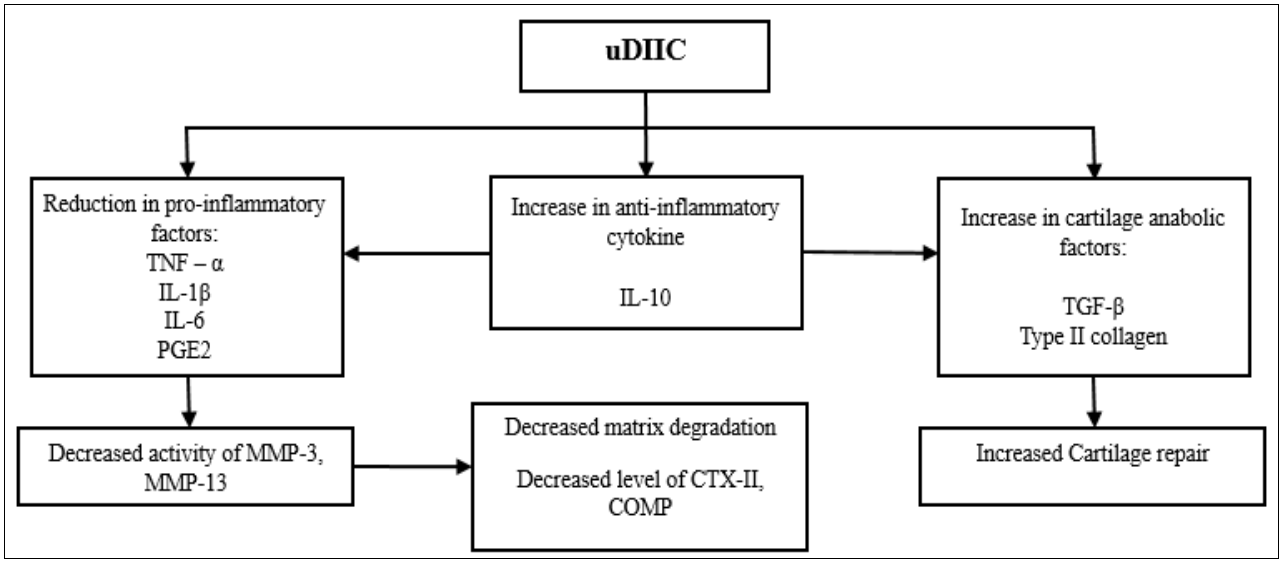
A study demonstrating that oral immunotherapy (OIT) using uDIIC, derived from chicken sternum cartilage, significantly protects against cartilage degradation in a murine model of CIA [43]. Administered prophylactically at a dose of 7.33 mg/kg three times per week, uDIIC reduced arthritis incidence by approximately 50% and preserved joint integrity in asymptomatic mice. Histopathological analysis revealed complete protection against cartilage and bone damage in these mice, with significantly lower histological scores for cartilage destruction (mean score ~0 vs. ~3.5 in CIA controls; p<0.001, Kruskal-Wallis test). Furthermore, immunofluorescence and flow cytometry analyses showed a marked reduction in IL-17 and IL-22 expression in joint tissues and draining lymph nodes of asymptomatic OIT mice, correlating with reduced Th17-mediated inflammation. These cytokines are known mediators of cartilage catabolism via upregulation of RANKL and osteoclastogenesis. Notably, the protective effects of uDIIC were not due to a reduction in anti-collagen antibody levels, indicating that the mechanism of action is not primarily humoral. Instead, the data suggest that uDIIC exerts its effects by modulating cellular immune responses—particularly by suppressing pro-inflammatory IL-17 and IL-22 cytokine production. This cytokine regulation likely prevents cartilage breakdown by inhibiting osteoclast activation and joint inflammation, highlighting a targeted immunomodulatory pathway rather than broad immune suppression [43].

Undenatured type II collagen in cartilage health-Clinical studies: A study conducted, 6-month prospective clinical study to assess the efficacy, tolerability, and cartilage-specific metabolic effects of undenatured type II collagen, in patients with knee OA (KL grade II-III). Statistically significant clinical improvements were observed as early as week 4, with a 5.3% and 9.1% reduction in Lequesne and Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores, respectively (p<0.01). These improvements were sustained and amplified over time, reaching a 25% reduction in Lequesne and 33.1% in WOMAC by week 24 (p<0.01 vs. baseline). Structurally, ultrasound analysis revealed progressive increases in femoral cartilage thickness: from 0.18±0.03 cm to 0.19±0.02 cm in the right knee (p<0.01), and from 0.17±0.03 cm to 0.20±0.03 cm in the left knee (p<0.01), indicating cartilage repair.

Metabolically, Urinary C-terminal telopeptide of type II collagen concentrations initially increased by week 4 (from 0.18±0.13 to 0.28±0.19 ng/mL, p<0.01), possibly reflecting matrix turnover, but subsequently decreased to 0.17±0.13 ng/mL by week 12 (p<0.01 vs. week 4), signifying reduced cartilage degradation. Importantly, 30% of patients who were taking Non-steroidal anti-inflammatory drugs (NSAIDs) at baseline discontinued their use during the study, further underscoring symptomatic relief. No adverse drug reactions were reported, and tolerability was rated as good in all cases. This multifaceted evaluation confirms that daily administration of 40 mg uDIIC over 24 weeks not only significantly alleviates clinical symptoms but also supports structural cartilage regeneration and downregulates biochemical markers of cartilage catabolism, establishing its role as a disease-modifying adjunct in knee OA management [44].

Discussion

Undenatured type II collagen is emerging as a promising nutraceutical intervention for joint health, particularly in the management of OA, which is characterized by progressive cartilage degradation, inflammation, and joint dysfunction. Unlike hydrolyzed collagen, UDIIC preserves its native triple-helical structure, which is essential for its immunological interaction and efficacy. UDIIC has been experimentally demonstrated to support cartilage health through the mechanisms illustrated in Figure 1.



[uDIIC = undenatured type II collagen, TNF-α = Tumour Necrosis Factor α, IL= Interleukin, PGE2 = Prostaglandin E2, MMP = Matrix Metalloproteinase, CTX-II = C-terminal cross-linked telopeptides of type II collagen, COMP = Cartilage oligomeric matrix protein, TGF-β= Transforming growth factor-β.]

Fig 1: Overview of uDIIC in supporting cartilage health through modulation of inflammatory and anabolic Biomarkers

A broad range of uDIIC sources have been investigated in preclinical models, including those derived from bovine, porcine, squid, chicken, and Nile tilapia. Among these, chicken-derived uDIIC especially from sternal cartilage has been most extensively studied and supported by the highest volume of preclinical and human research. However, the most robust and consistent findings have come from studies using chicken-derived uDIIC, including those conducted in rodent and canine OA models. In contrast to the wealth of preclinical data, clinical studies in humans remain limited. Among the fourteen total studies identified in the literature, six used undenatured collagen type II developed by Lonza Inc., USA, marketed under the name UC-II® [33, 35, 37, 39, 43, 44]. This subset of research consistently reports beneficial effects on cartilage health, systemic inflammation, and functional joint parameters, across both preclinical and clinical contexts. Importantly, these studies reinforce the reproducibility, safety, and efficacy of the specific UC-II® formulation.

Despite encouraging results from both mechanistic and clinical investigations, it must be emphasized that only pilot-level clinical evidence is currently available in humans. Most studies are small-scale, of short duration, or open label in design. Therefore, there remains a critical need for well-designed, large-scale, randomized, double-blind, placebo-controlled clinical trials to validate these findings, explore therapeutic mechanisms in diverse patient populations, and assess long-term benefits.

Conclusion

Undenatured type II collagen presents a promising immunomodulatory approach to osteoarthritis by targeting inflammatory pathways and supporting cartilage preservation. While preclinical data robustly support its efficacy, current clinical findings remain preliminary. To fully establish uDIIC as a disease-modifying agent in OA, comprehensive large-scale, randomized controlled trials are essential. Its potential to improve joint health and slow disease progression offers hope for advancing OA management beyond symptomatic relief.

Acknowledgement

UC-II® is registered trademark of Lonza Inc., USA.

Conflict of Interests

Tanya Bhagat, Dr Atul Sharma, Dr. Prashant Narang, are on the payroll of Haleon India. For the remaining authors, none were declared.

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