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Review Article

Efficacy of undenatured collagen in knee osteoarthritis: review of the literature with limited meta-analysis

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Abstract: Background: Early knee osteoarthritis (OA) treatment is multimodal, with physical therapy and pharmacotherapy commonly used. Although popular, oral supplements like glucosamine and diacerein have not been reported to have high efficacy. Undenatured collagen type II (UC-II) has been introduced for therapy in early OA; it helps in cartilage repair and preservation. The present review was done to ascertain its efficacy in pain relief and knee function. Materials and methods: A systematic literature search was performed on MEDLINE (PubMed), Embase, Scopus, and Cochrane Library for published literature; studies comparing the outcome of UC-II supplementation with placebo/control in adult humans with early knee OA were included. The outcomes evaluated were VAS Score, quality of life - *Western Ontario and McMaster Universities* (WOMAC-score), Knee function, Knee range of motion, and any complications during the course of treatment. Results: A total of 293 results were obtained after a primary search; 8 randomized control trials (RCT) were finally included. A total of 243 patients received UC-II supplementation (91 men and 152 women). The overall mean age range for the intervention group was 53.5±0.99 to 68.7±5.3 years across all included studies, and the mean follow-up duration was 3 to 6 months. Outcome measures like WOMAC and VAS scores showed better outcomes with UC-II in comparison to placebo. Walking measurements improved significantly from the baseline, reflected in improved timed up-and-go and 6-minute walk tests (6MWT). The overall complications were similar to other supplements. Conclusion: With limited literature, UC-II has shown promise as a potent supplement in early knee OA with good pain relief and improved function. However, further large-scale studies are needed to substantiate these findings.

Keywords: Knee osteoarthritis, native type II collagen, undenatured type II collagen, WOMAC, visual analog scale, Lequesne's functional index

Introduction

The prevalence of osteoarthritis OA of the knees among the elderly is 28.7% in the Indian population [1]. The disease's severity and effects on quality of life can vary from mild to severe. Common symptoms include discomfort that gets worse with movement or exercise, joint stiffness, and the inability to squat or sit cross-legged [2, 3].

OA treatment strategies include home-based physical therapy, physiotherapy, medications, and joint replacements in severe conditions [4, 5]. Commonly used medications for knee OA include over-the-counter pain relief medicines like acetaminophen and Non-Steroidal Anti-inflammatory Drugs (NSAIDs). These help in the alleviation of pain, but this effect is temporary, and these have no effect on the disease process [6]. Despite being effective in pain management, prolonged use of these medications can have adverse effects such as nephrotoxicity, hepatotoxicity, and gastric ulcers. Other dietary supplements are frequently prescribed and consumed with the aim of disease modification, but their role is unproven. Glucosamine and chondroitin sulphate (G+C) are the most commonly used agents [6]. The latest American Academy of Orthopaedic Surgeons and American College of Rheumatology guidelines for treating knee osteoarthritis have given a limited recommendation for using these oral supplements [4, 7].

Table 1. Literature search criteria used

Database	From the period of inception to 9th October 2022 with keywords	Results
MEDLINE (PubMed)	((("indigenous peoples"[MeSH Terms] OR ("indigenous"[All Fields] AND "peoples"[All Fields]) OR "indigenous peoples"[All Fields] OR "natives"[All Fields] OR "native"[All Fields] OR "natives"[All Fields] OR "natively"[All Fields] OR "nativeness"[All Fields] OR "nativity"[All Fields]) AND ("collagen type ii"[MeSH Terms] OR ("collagen"[All Fields] AND "type"[All Fields] AND "II"[All Fields]) OR "collagen type ii"[All Fields] OR ("type"[All Fields] AND "II"[All Fields] AND "collagen"[All Fields]) OR "type ii collagen"[All Fields])) OR (("undenaturated"[All Fields] OR "undenatured"[All Fields]) AND ("collagen type ii"[MeSH Terms] OR ("collagen"[All Fields] AND "type"[All Fields] AND "II"[All Fields]) OR "collagen type ii"[All Fields] OR ("type"[All Fields] AND "II"[All Fields] AND "collagen"[All Fields]) OR "type ii collagen"[All Fields])) OR ("UC"[All Fields] AND "II"[All Fields])) AND ("osteoarthritis, knee"[MeSH Terms] OR ("osteoarthritis"[All Fields] AND "knee"[All Fields]) OR "knee osteoarthritis"[All Fields] OR ("knee"[All Fields] AND "osteoarthritis"[All Fields]))	56
Embase	(native AND type AND ii AND collagen OR (undenatured AND type AND ii AND collagen) OR 'uc ii') AND 'knee osteoarthritis'	20
Scopus	(ALL (undenatured AND type AND ii AND collagen) OR ALL (uc-ii) AND ALL (knee AND osteoarthritis))	185
Cochrane Library	Undenatured type II collagen in All Text OR i UC-II* in All Text OR Native Type II Collagen in All Text AND knee osteoarthritis in All Text - with Publication Year from 2000 to 2022, in Trials (Word variations have been searched)	32
Total		293

A more recent compound that has shown promise in treating early OA is UC-II, which is produced from chicken sternal cartilage [8, 9]. Its usage in rheumatoid arthritis (RA) patients was the subject of the first research, but more recent research has concentrated on its effectiveness in treating primary OA [10]. The first UC-II for knee OA in a human experiment was published by Crowley et al. [11]. They discovered that UC-II reduced pain and the WOMAC score more effectively than G+C. In order to determine the results and symptomatic improvement with this therapy modality, this study aimed to review the existing literature on the use of UC-II in knee OA.

Methods

Study design

This systematic review followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12].

Search strategy

Two authors (RKR and PK) independently conducted a primary electronic search on the databases of MEDLINE (PubMed), Embase, Scopus, and the Cochrane Library for the published literature from the year of inception to October 9, 2022, without the initial restriction of language or country of publication, using a predetermined search strategy developed previously (**Table 1**). A secondary search of the bibliographies of the papers initially included in the first search and a bibliography of review articles was conducted to find additional research articles. Finally, 293 results were discovered.

Inclusion and exclusion criteria

Studies that assessed the effects of UC-II supplementation for knee osteoarthritis were either prospective or retrospective in English. Case reports, conference abstracts, e-posters, book chapters, review articles, animal studies, and publications in languages other than English were all disqualified.

PICO framework for the study

Participants: Adults human with knee osteoarthritis. Intervention: Oral supplementation of UC-II. Control: None/placebo. Outcomes: VAS Score, quality of life (WOMAC-score), Knee functionality, range of motion, and any complications during treatment.

Study selection

Three authors (PK, MSD, and SS) independently assessed all the papers based on their titles and abstracts, and one linked to the study question was found. Then, depending on the inclusion and exclusion criteria, their entire texts were obtained, and pertinent research was added to the current review. Any disagreements amongst the writers were settled through consensus.

Table 2. Characteristics of included studies

Sl no.	Author/year	Study design	Level of evidence	Treatment Groups	Number of patients	Male/ female	Mean age (year) with SD	BMI	KL Stage/ Ahlback grade	Follow up in months
1	Crowley et al. 2009 [11]	RCT	I	UC-II	26	13/13	58.9±9.79	NR	NR	3
				G+C	26	17/9	58.7±10.3	NR	NR	3
2	Lugo et al. 2015 [13]	RCT	I	UC-II	63	33/30	53.5±0.99	25.2±0.37	II-42, III-21	6
				GC	65	28/37	52.6±1.02	25.5±0.40	II-45, III-20	6
				Placebo control	58	28/30	53.1±1.02	24.7±0.40	II-39, III-19	6
3	Bakilan et al. 2016 [14]	RCT	I	AC+CII	20	1/19	57.65±8.73	30.20±5.27	II-16, III-4	3
				AC	19	2/17	58.84±6.55	27.9±4.16	II-18, III-1	3
4	Costa et al. 2020 [15]#	RCT	I	CPG	20	6/14	55.45±8.78	30.15±4.85	I-1, II-12, III-7	6
				PCPG	20	4/16	57.35±11.44	30.34±5.66	I-2, II-10, III-8	6
5	Costa et al. 2021 [16]*	RCT	I	UC-II (CG-group)	20	7/13	60.25±7.45	26.95±3.84	I-2, II-11, III-7	6
				Placebo	20	6/14	57.60±6.96	30.01±4.47	I-4, II-7, III-9	6
6	Rui et al. 2021 [9]	RCT	I	UC-II	28	13/15	59.40 (4.9)	22.60 (1.8)	I-17, II-11	3
				PC	27	11/16	61.61 (1.3)	23.80 (2.2)	I-16, II-11	3
7	Sadigursky et al. 2022 [17]	RCT	II	UC-II	53	18/35	68.7±5.3	27.9±2.4	II-22, II-31	3
				Control	52	18/34	68.6±6.0	27.9±1.5	II-20, II-32	3
8	Santana et al. 2022 [18]	RCT	I	UC-II	13	0/13	54.1±7.9	29.6±5.2	Ahlback 2-4	3
				Control	13	0/13	61±6.6	33.1±7.3	Ahlback 2-4	3
				EG	13	0/13	60±10.8	35.3±6.6	Ahlback 2-4	3

RCT-Randomized control trial, UC-Undenatured Collagen, GC-Glucosamine HCl+Chondroitin Sulfate, AC+CII-Acetaminophen + Native Type II Collagen, AC-Acetaminophen, CPG-collagen + physiotherapy group, PCPG-placebo collagen + physiotherapy group, PC-positive control group, EG-exercise group. #out of 3 groups only two groups shown here relevant tour review. *out of 5 groups in the study we have included only two groups relevant to our review. BMI-Body mass index.

Data extraction

RKR, PK, and SP, three independent authors, independently extracted the data from each included article and entered them in a table with the authors' names, the year, the level of evidence, the total number of patients, the length of follow-up, the degree of knee alignment, the body mass index (BMI), relevant demographic information, Kellgren-Lawrence (K-L)/Ahlback's grades, and the primary and secondary outcome (**Tables 2**, **3**). The authors of the current review carefully read and assessed each of the final papers in order to minimize any potential operator-dependent bias. Data from 8 studies that were relevant to the research question were evaluated (**Figure 1**) [9, 11, 13-18].

Outcome measure

The primary outcomes were patient-reported outcomes - Pain assessed by Visual Analog Scale (VAS), quality of life - WOMAC, Lesquene's functional index (LFI), knee functionality assessed by timed up and go (TUG) test and 6MWT, and knee range of motion. The secondary outcomes were complications during and/or related to treatment.

Statistical analysis

The Review Manager Software, version 5.4, was used to conduct the statistical analysis [19]. When two studies had the same outcome, a meta-analysis was conducted. Odds ratio (OR) was utilized for dichotomous data, and mean difference (MD) was employed for continuous variables to evaluate treatment effects. For each result, a 95% confidence interval was displayed. Forest plots were used for each outcome of interest to produce a visual summary. The numerous causes of clinical heterogeneity were also looked at. The I^2 test was employed to assess statistical heterogeneity. If the heterogeneity was deemed to be low, a fixed-effects model was utilized; otherwise, a random-effects model was used.

Risk of bias assessment

Using the risk of bias tool for RCTs developed by The Cochrane Collaboration, three reviewers (VK, MSD, and SP) independently evaluated the risk of bias in the included papers [20].

Table 3. Studies reporting outcome data

Sl no.	Author/ year	Treatment Groups	VAS score		WOMAC		Lequesne Score		Knee Range of Motion		TUG		6-MWT		Adverse events
			Base line	End point	Base line	End point	Base line	End point	Base line	End point	Base line	End point	Base line	End point	
1	Crowley et al. 2009 [11]	UC-II	NR	40% Reduction	NR	33% Reduction	NR	15% Reduction	NR	NR	NR	NR	NR		35
		G+C	NR	15% Reduction	NR	14% Reduction	NR	6% Reduction	NR	NR	NR	NR	NR		58
2	Lugo et al. 2016 [13]	UC-II	58.4±0.99	Significant Decrease UC-II vs. placebo	58.1±1.03	24.0±1.23 Reduction in mean WOMAC 22.5±1.20	7.90±0.13	UC-II versus placebo (2.9 vs. 2.1), UC-II versus GC (2.9 vs. 2.2)	114±1.57		NR	NR	NR		NR
		GC	59.1±0.97	NR	57.5±1.33	19.2±1.20	8.02±0.12		114±1.36		NR	NR	NR		NR
		Placebo control	58.2±0.97	NR	56.9±1.36	17.0±1.25	7.74±0.12		114±1.62		NR	NR	NR		NR
3.	Bakilan et al. 2016 [14]	AC+CII	4 (0-9)	2 (0-10)	53.5 (29-98)	44 (24-89)	NR	NR	NR	NR	NR	NR	NR		NR
		AC	3 (0-8)	3 (0-8)	50 (28-103)	52 (24-102)	NR	NR	NR	NR		NR			NR
4	Costa et al. 2020 [15]	CPG	6.42±1.68	3.26±2.88	45.25± 17.88	24.11± 24.5	11.18±3.30	7.08±5.97	117.1±13.71-R 114.85±14.42-L	124.00±14.13 124.42±12.64-L	11.53±3.51	9.24±3.91	301.38± 92.21	372.10± 145.04	NR
		PCPG	5.60±2.11	3.05±2.82	43.00± 20.21	27.05± 24.76	11.20±3.45	8.75±6.30	118.80±17.06-R 122.00±16.88-L	120.30±14.68 122.50±14.20-L	11.56±4.26	9.93±3.14	No significant change		NR
5	Costa et al. 2021 [16]	CG	NR	NR	34.9±16.2	15.8±15.8	9.6±2.6	4.7±4.1	NR		8.88±2.60	8.01±2.61	325.4±71.7	371.0±70.6	NR
		Placebo control	NR	NR	34.9±20.6	29.7±20.1	10.7±5.0	9.4±6.0	NR		11.28±4.99	11.04± 4.34	308.2± 89.67	309.6±88.8	NR
6	Rui et al. 2021 [9]	UC-II	3.43±1.9	2.11±1.6	56.02±12.1	36.00±7.6	NR	NR	57.9 ±14.0	66.9±10.4	NR	NR	NR		NR
		Placebo control	3.10±1.98	2.91±2.3	50.12±10.1	47.61±7.6	NR	NR	51.8±15.2	52.4±10.7	NR	NR	NR		NR
7	Sadigursky et al. 2022 [17]	UC-II	7.1±0.9	3.4±1.6	54.0±16.6	44.6±12.0	NR	NR	NR	NR	NR		NR		NR
		Control	7.3±0.7	6.0±1.8	58.6±14.3	57.3±16.5	NR	NR	NR	NR	NR		NR		NR
8	Santana et al. 2022 [18]	UC-II	NR	NR	55.6±3.6	38.0±6.3	NR	NR	105.4±5.4	113.4±3.6	7.5±0.2	6.6±0.1	403.8±12.5	445.7±10.3	NR
		Control	NR	NR	60.4±4.8	51.1±4.7	NR	NR	100.0±3.7	97.8±3.4	12.1±0.7	2±0.3	316.1±21.0	334.8±13.2	NR
		EG	NR	NR	48.4±6.4	26.2±6.3	NR	NR	102.7±4.1	110.0±3.7	12.4±1.1	7.9±0.5	344.7±23.7	407.4±16.3	NR

VAS-Visual Analog Scale, WOMAC-Western Ontario and McMaster Universities, NR-Not Reported, TUG-Timed Up and Go test, 6MWT-6-minute walk test, R-Right Knee, L-Left Knee.

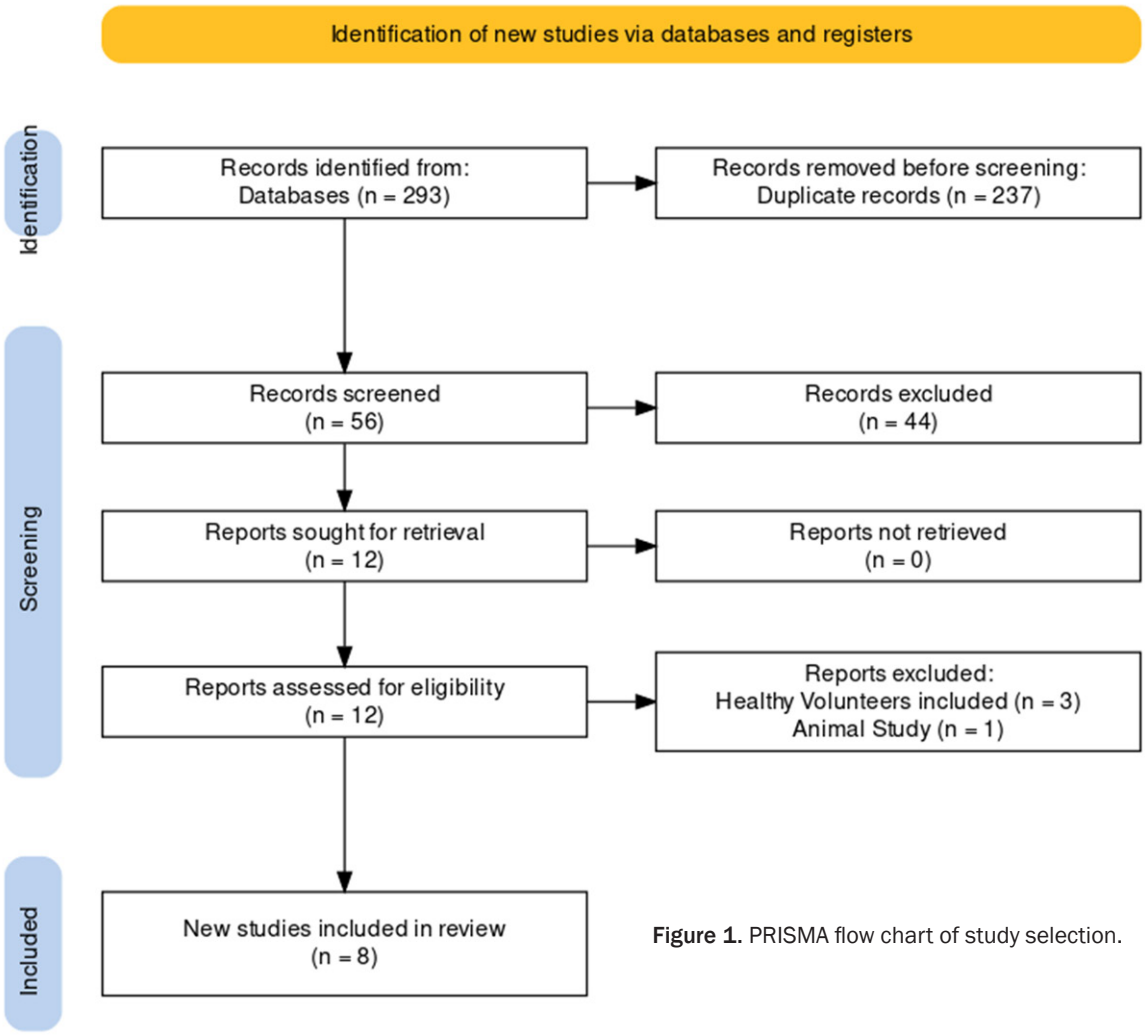

Figure 1. PRISMA flow chart of study selection.

Results

Search and screening

A primary search yielded 293 items from the four databases combined. After removing duplicates and studies not relevant to our study, 56 studies were found for further investigation. Twelve papers were chosen after carefully examining their titles and abstracts, and their entire texts were evaluated for inclusion in the present review. Finally, 8 published articles were included in the analysis (**Figure 1**) following a thorough review.

Characteristics of the included studies

All 8 studies included in the current review were RCTs [9, 11, 13-18]. All articles included in the review were Level I/II comparative studies. Crowley et al. [11] compared the UC-II alone as a supplement with G+C. Lugo et al. [13] used three groups that received daily UC-II, G+C, and placebo. Acetaminophen (AC) and native type II collagen supplementation were contrasted with AC supplementation alone by Bakilan et al. [14]. In a subsequent study, Costa et al. 2021 [16] compared five patient groups: UC-II supplementation (CG-group), placebo UC-II (PCG-group), UC-II and neuromuscular electrostimulation (NMES) strengthening (CNSG-group), and NMES Strengthening (NS). Costa et al. 2020 [15] evaluated three groups of supplementation UC II and physical therapy group (CPG), placebo UC-II.

Rui et al. [9] compared UC-II with placebo control groups. Sadigursky et al. [17] compared groups that were supplemented with UC-II and the control group that was not. Santana et al.

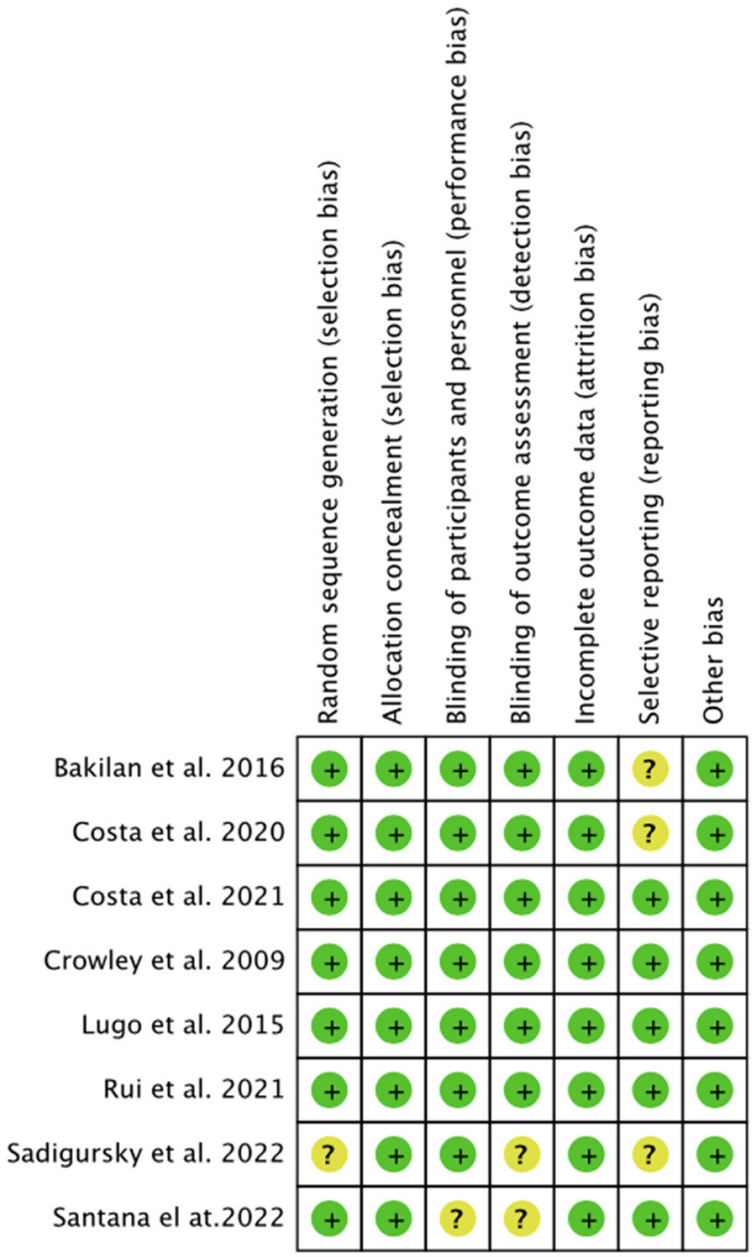

Figure 2. Risk of bias summary of included studies.

[18] included and compared three groups: UC-II, an exercise group (EG), and a control group. The treatment groups and comparisons are shown in **Table 2** for the studies included in the current review.

A total of 243 patients with knee osteoarthritis received UC-II supplementation, with 91 males and 152 females. The overall mean age ranged for the intervention group from 53.5±0.99 to 68.7±5.3 years across the 8 included studies. The patients' mean BMI ranged from 22.6±1.8 to 30.20±5.27. The mean follow-up duration was 3 to 6 months. K-L grading was reported on 6/8 and included studies [9, 13-17], and Ahlback grade in 1/8 study [18]. K-L grade distribution for the included patients in the intervention group was I-20, II-104, and III-70 shown in **Table 2**.

Drug schedule

In a trial by Crowley et al. [11], subjects in the UC-II group received 2 capsules from Inter Health Nutraceuticals, Inc., Benicia, CA, each containing 20 mg of UC-II and 5 mg of the bioactive undenatured component. Two capsules containing 20 mg of UC-II each were given to the patients by Lugo et al. [13], for a total of 40 mg. This dosage gave the patient 1.2 mg of the active substance. The study group in the experiment by Bakilan et al. [14] got 10 mg/day of natural type II collagen (Bioiberica S.A., Spain) and 1500 mg/day of acetaminophen. In both experiments [15, 16], Costa et al. gave participants a daily dose of 40 mg of UC-II collagen containing 10 mg of the bioactive substance. Rui et al. [9] supplemented all patients in the UC-II group with 2 capsules containing 20 mg of each undenatured collagen (SEMNL, Inc., Beijing, China). Sadigursky et al. [17] administered 40 mg of UC-II daily in the study group of patients. Santana et al. [18] administered one capsule per day of UC-II (Motilex Caps®, Apsen Pharmaceutics, Santo Amaro, Sao Paulo, Brasil).

Assessment of risk of bias

Eight included RCTs [9, 11, 13-18] have a low assessed risk of bias. **Figures 2** (risk of bias

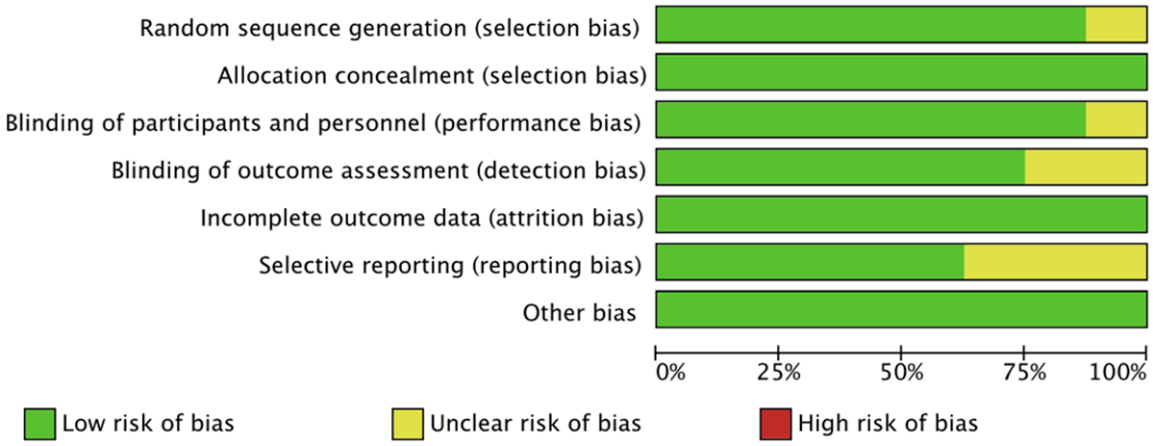

Figure 3. Risk of bias graph of included studies.

summary) and **3** (risk of bias graph) demonstrate the risk of bias evaluation of all included studies.

Primary outcomes

Visual analog scale (VAS) for pain: Pain VAS scores were recorded in five out of the eight studies' evaluations [11, 13, 15, 17]. Both treatments were successful in reducing VAS scores, although UC-II was more successful with a 40% decline after 90 days of treatment compared to a 15% drop in the G+C treated groups, according to Crowley et al. [11]. Further group analysis showed that G+C cohorts significantly decreased their VAS scores relative to baseline values after 30 days, but not at 60 or 90 days of supplementation. UC-II cohorts, on the other hand, displayed a significant decline in VAS scores at Days 60 and 90 compared to Baseline. According to Lugo et al. [13], the mean VAS score for the UC-II supplementation group at the final follow-up of 6 months was significantly lower than that of the GC (22.6 vs. 18.4) and placebo (22.6 vs. 17.0) groups. According to Bakilan et al. [14], there was a 50% drop in the VAS score for the AC+CII group compared to the AC group, which was a significant change. After 30 days of the intervention, Costa et al. 2020 [15] discovered a considerable decrease in pain in all groups. This reduction persisted until the final follow-up, and there were never any disparities between the groups during the course of the trial. There was a substantial difference between the two groups, according to Sadigursky et al. [17], with the UC-II group experiencing a higher decline in VAS score throughout the course of the study's 90 days.

WOMAC score: In each of the eight investigations, the WOMAC score was given. After 90 days of therapy, Crowley et al. [11] discovered that UC-II treatment had the greatest effect lowering the WOMAC score (by 33%) compared to the G+C group (by 14%). Further group analysis revealed that UC-II groups showed a statistically significant improvement in WOMAC score as compared to participants who received G+C, who showed no significant change in WOMAC score at 90 days of treatment.

In comparison to the placebo group, patients receiving UC-II experienced a significant decrease in all three WOMAC score subscales (pain, stiffness, and physical function), according to Lugo et al. [13]. At 180 days of follow-up, the total WOMAC score for the UC-II group was considerably lower than for the GC group. According to Bakilan et al. [14], after 3 months of treatment, patients receiving AC+CII reported significant improvements in their WOMAC pain, total, and physical functional scores when compared to a group of patients receiving AC.

Costa et al. 2020 [15] demonstrated a reduction in WOMAC score in all intervention groups with no significant differences between them at 6 months of follow-up. Costa et al. 2021 [16] found that in the CG group of patients, the subjective functional score evaluated by WOMAC score had improved at day 30 of assessment and kept on improving until the final follow-up, whereas the placebo group (PCG) did not show

significant improvement in WOMAC functional score during the study period.

In the comparison by Rui et al. [9], the WOMAC sub-score and sum decreased significantly in the UC-II treatment group, and this decrease was significantly greater than that in the placebo group. A similar finding was reported by Sadigursky et al. [17] in all WOMAC sub-score and the overall score. Santana et al. [18] also had similar findings for the WOMAC score.

LFI score: LFI scores have been reported for four of the eight included studies. Crowley [11] noted that from baseline to day 90, the total LFI score was significantly lower in the patients receiving UC-II treatment than it was in the G+C group of participants at all treatment time periods examined.

In comparison to the placebo and GC groups, the LFI score for the UC-II treated group was significantly lower after day 180 of treatment, according to Lugo et al. [13]. The LFI subscale for everyday activities was significantly lower for the UC-II group at day 180 compared to day 180, which helped to improve the group's overall LFI score.

All groups' LFI scores dropped; however, the CPG and PG showed lower values at 30 days, according to Costa et al. 2020 [15]. The LFI score for the CG group had significantly improved after 30 days of evaluation, and it continued to rise until the final follow-up, according to Costa et al. 2021 [16]. However, they did not exhibit any appreciable changes in function throughout the course of the six-month study period in the PCG group.

TUG test: Functional mobility was assessed by the TUG test in three of the eight studies [15, 16, 18]. Costa et al. [15] observed that all treatment groups showed an initial decrease in TUG test execution time after 30 days; however, it was maintained only in the CPG and PG groups at six months of assessment.

In another study, Costa et al. [16] found a similar outcome for the TUG test at 6 months of follow-up for undenatured collagen supplementation.

According to Santana et al. [18], all three groups significantly improved at the final evaluation compared to the initial exam, and the test's duration was cut in half. When compared to the CG group, the EG and MG groups greatly outperformed it, but there was no evidence of superiority between the MG and EG groups, according to an intergroup comparison.

6MWT: Out of the eight trials that were considered, 3-MWT was reported [15, 16, 18]. Only the CPG increased the distance traveled in all measures when compared to other treatment groups, according to Costa et al. [15]. Similar results of improvement in 6 MWT at the final follow-up in the collagen-supplemented group were found by Costa et al. in their previous study [16]. When Santana et al. [18] compared the 6 MWT value in the EG and UC-II groups to the value from the initial evaluation, they found a significant change. Intergroup analysis revealed that both the EG and UC-II groups significantly improved when compared to the CG group, but there was no difference between the EG and UC-II groups.

Knee range of motion (ROM): Only four studies examined changes in knee ROM following therapy. The study by Lugo et al. [13] did not include any data, although they did indicate that there was no significant difference in knee ROM across the study groups. The active and passive bilateral knee ROM across the study groups was not significantly different, according to Costa et al. 2020 [15]. The range of motion increased substantially more following treatment with UC-II, according to Rui et al. [9] (p-value = 0.078). The collagen-supplemented group showed a considerable improvement in knee range of motion for flexion in comparison to the control group, according to Santana et al. [18].

Secondary outcomes

Crowley et al. [11] recorded 58 adverse events in the G+C group of participants over the 90-day research period and 35 in the UC-II group. In terms of severity, 43% of the UC-II group's adverse events were mild, compared to 54% of the group's moderate events and 60% and 38% of the G+C group's moderate events, respectively. While G+C individuals experienced bloating, pain abdomen, rash, edema around the eyes, hives on the face and chest, and headache, UC-II subjects frequently experienced constipation and intermittent headache. The two therapy groups did not sig-

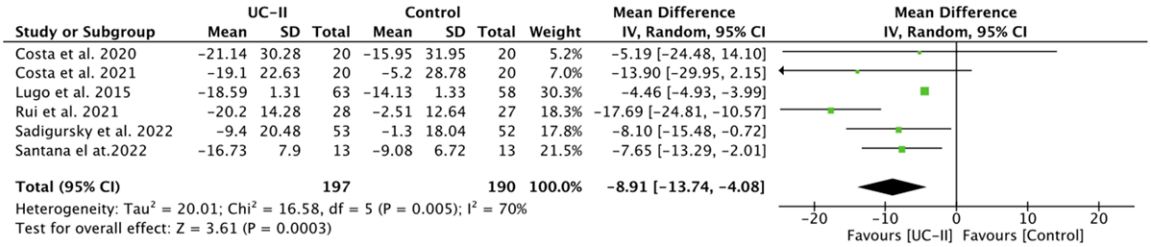

Figure 4. Forest plot comparing WOMAC scores. WOMAC-Western Ontario and McMaster Universities.

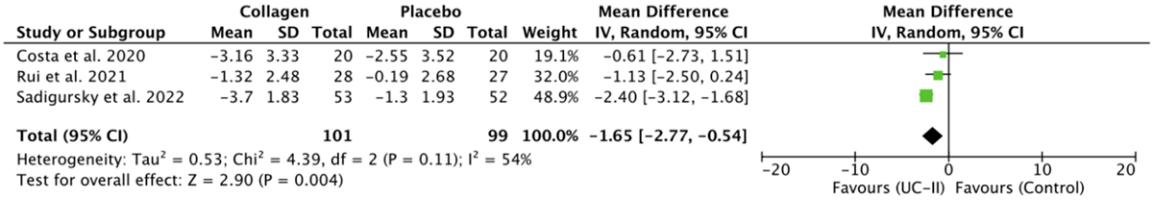

Figure 5. Forest plot comparing VAS pain scores. VAS-Visual Analog Scale.

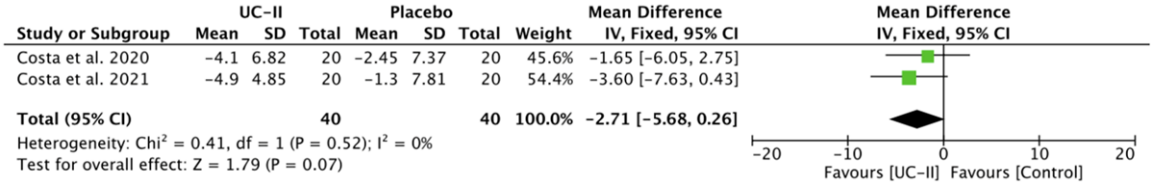

Figure 6. Forest plot comparing Lesquene's functional index.

nificantly differ in terms of adverse events, though.

Results of meta-analysis

We evaluated the results of undenatured collagen vs. a placebo control using the information at hand. According to a meta-analysis, undenatured collagen supplementation significantly improved WOMAC scores compared to the placebo control group (MD -8.91 [95% CI -13.74, -4.08; P = 0.05]) (**Figure 4**). Similarly, VAS showed significant improvement as well (MD -1.65 [95% CI -2.77, -0.54; P<0.05]) (**Figure 5**). However, no significant difference occurred in improvement in LFI scores between undenatured supplementation and placebo control, which were analyzed only for two studies (MD -2.71 [95% CI -5.68, 0.261; P = 0.52]) shown in **Figure 6**.

Discussion

This review and meta-analysis were conducted to ascertain UC-II supplementation's efficacy in ameliorating the symptoms, decreasing pain, and improving function in individuals suffering from early knee OA. We determined that as per the published literature, UC-II has shown good results with significantly decreased VAS scores, decreased WOMAC knee scores, and improved knee function on TUG-test and 6MWT.

Even though pharmacologic treatments like G+C are frequently used to treat knee OA, the majority of recently updated clinical practice guidelines advise against using them to halt the disease's progression and reduce symptoms. The highest grade of evidence in terms of pharmacologic support for OA exists for topical/oral NSAIDs, acetaminophen, and opioids for pain relief and to promote physical activity and home based exercises [4-7]. Native type II collagen (UC-II) derived from chicken sternal cartilage is a novel therapy that possibly acts by desensitizing the T-cell mediated attack on native type II collagen and can thus help prevent joint inflammation and degradation [21]. Animal studies on the use of UC-II have shown a positive effect on preventing cartilage damage and arresting the

advancement of the disease process [22-25]. In human studies, it has been effective in cases of rheumatoid arthritis and in healthy volunteers with knee pain, leading to its postulation as a possible therapy for knee OA [10, 26-28].

In our review, the most commonly used dosage of UC-II was 40 mg/day, resulting in about 10 mg of bioactive compound used daily. This is the standard accepted dosing regimen for UC-II and is the one for which we have tried to determine effectiveness in reducing joint pain, improving knee function, and decreasing WOMAC score. After therapy, the majority of the trials we reviewed showed a statistically significant reduction in the VAS scores for pain, and this difference was much larger than it was for the control groups. The reduction in WOMAC ratings of participants in the study groups showed similar trends, with those receiving UC-II experiencing higher drops from baseline. The greatest effect has been seen on the measurements related to walking (VAS walking and WOMAC function). Improvement in walking status can lead to increased physical activity (TUG-test and 6MWT showed) and a resultant improvement in symptoms of OA.

Despite the possible effectiveness of UC-II in the treatment of OA, large-scale evidence is not available to ascertain this. On review of all the available literature, we were able to report findings of only 293 patients enrolled in various studies. While treatment with UC-II could possibly be one of the first widely accepted nutraceuticals for use in OA, large-scale multicentric RCTs are needed to substantiate the findings.

Disclosure of conflict of interest

None.

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