

Effects of UC-II, Glucosamine, and Curcumin Supplementation on Knee Pain

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ABSTRACT

Knee joint pain is a common cause of disability, with risk factors including aging, obesity, and occupational joint loading. Because long-term use of conventional analgesics can lead to adverse effects, low-risk nutraceutical options are of growing interest. Undenatured type II collagen (UC-II) has shown symptomatic benefit in randomized trials, while glucosamine and curcumin have demonstrated pain-reducing, synovial-supporting, and anti-inflammatory effects in systematic reviews. In this study, we evaluated the efficacy of a UC-II+glucosamine+curcumin combination for reducing knee joint pain and improving function. A two-arm, parallel-group, randomized, double-blind, clinical trial enrolled 32 adults with knee pain who received either a placebo or the test product for 12 weeks (two capsules daily). The capsules of the placebo group contained UC-II only, whereas those of the test group contained UC-II, glucosamine, and curcumin. Assessments at weeks 0, 6, and 12 included a visual analog scale (VAS), timed up-and-go (TUG), active/positive range of motion (AROM/PROM), and the Western Ontario and McMaster Universities Arthritis Index (WOMAC). Both groups showed improvements in knee pain. In the test group, the TUG time significantly decreased and knee ROM increased by week 6. Supplementation with the UC-II+glucosamine+curcumin combination was associated with observable pain reduction and functional improvement of the knee joint.

Keywords

Knee pain, Curcumin, Glucosamine, UC-II.

Introduction

Arthritis is a disease caused by inflammation in one or more joints, characterized by pain, stiffness, especially in the early morning or after exercise, swelling, deformation, and decreased mobility [1]. Osteoarthritis (OA) is caused by the abnormal destruction of

cartilage at the ends of the bones, and some cases are due to injury or congenital anomalies of proteins that make up cartilage [2,3]; it usually appears in joints that bear weight loads such as the spine, knees, hips, and hands. In general, sex, aging, a diet imbalance, and an abnormal lifestyle, such as long-term work that puts pressure on knee joints and sports damage, are causes of OA [4-6]. As friction within the articular cartilage increases, the normal cartilage surface becomes progressively roughened. Fissures

develop in the superficial zone, leading to detachment of small cartilage fragments. These changes contribute to an increasingly irregular articular surface, which may further exacerbate joint degeneration [7], and the symptoms usually begin with pain, stiffness, and swelling. As OA advances, pathological changes extend from cartilage degradation to marginal bone remodeling, including the formation of osteophytes. These bony outgrowths are readily identifiable through radiographic imaging and are considered a hallmark of structural joint degeneration [8,9]. Although OA most commonly presents in individuals in their 40s and 50s, it can also affect younger people [9,10]. Occupations or activities that impose prolonged loading or compression on the joints, such as competitive sports or construction work, as well as prior joint injury or trauma, increase the risk of developing OA [6]. Patellofemoral pain is principally related to imbalanced muscular loading and typically affects adults under 40 years of age and physically active adolescents. Meniscal tears may arise from acute sports-related trauma or degenerative changes within the meniscus [11]. Each of these conditions can cause knee pain, so early recognition of these risk factors in younger populations is important.

Although OA pain can be relieved by drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, their side effects limit long-term use [12,13]. Thus, increasing attention has been given to non-pharmacological options. Undenatured type II collagen (UC-II) was confirmed to provide flexible care of joints for higher efficiency and long-lasting effects [14]; glucosamine can stimulate hyaluronic acid synthesis, thereby enhancing synovial fluid production and relieving pain [15] and curcumin can ameliorate inflammation [16]. The aim of this study was to compare whether a combined supplement of VITABOX® U.S. patented UC-II®+high-efficiency glucosamine+C3 super curcumin was more effective than UC-II alone in improving knee pain.

Materials and Methods

Study design

This was a two-arm, parallel-group, 12-week, randomized, placebo-controlled trial (Figure 1). All participants provided informed consent before the study began. The study was approved by Clinicaltrials no.: N202406039.

Recruitment

Participants were recruited from throughout Taiwan using social media. The recruitment time was from May to August 2024. Interested participants were randomly assigned to the UC-II placebo group or the turmeric complex group.

Intervention

One dose consisted of two capsules. Two UC-II placebo capsules contained 42 mg UC-II, while two turmeric complex products contained 42 mg UC-II, 460 mg glucosamine, and 380 mg curcumin. Both the placebo and turmeric complex products were provided by VITABOX® (Taipei, Taiwan). Participants in each group were requested to take two capsules 2 hours after breakfast or lunch, and any remaining capsules were enumerated

to determine compliance.

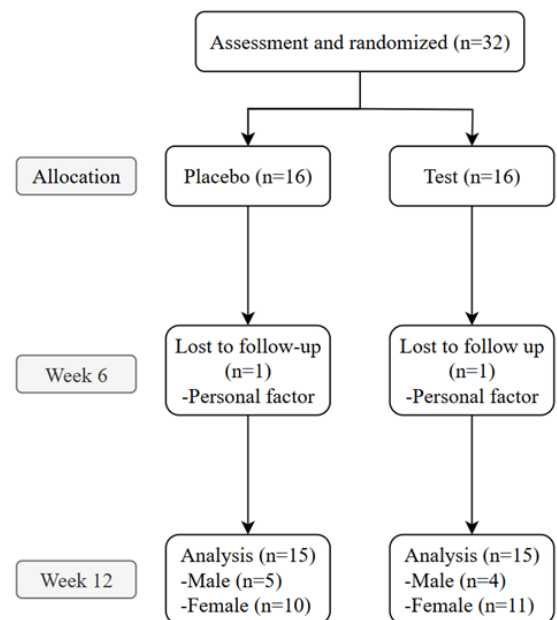


Figure 1: Flow chart.

Blood test

All participants were asked to fast for at least 8 hours prior to having 10 mL of blood drawn at Taipei Medical University Hospital. Blood collection was performed at the baseline (week 0), week 6, and week 12.

Visual analog scale (VAS)

Pain intensity was assessed using a 10-cm horizontal VAS, which is a psychometric response scale commonly used to quantify subjective sensations such as self-assessed pain in the following items: normal walk, stand up/squat down, and bend to the largest angle. The VAS was presented as a 10-cm line anchored at the left end with “0 = no pain” and at the right end with “100 = worst imaginable pain”. Participants were asked to mark their pain level on the line, and data were recorded at the baseline (week 0), week 6, and week 12.

Timed Up-and-go (TUG) Test

Knee joint activity was evaluated using the TUG test and was carried out by a professional physical therapist. An armless chair with a straight back was placed with a clearly marked line 3 m directly in front of the chair. On the physical therapist’s command of “go”, the participant rose from the chair, walked to the 3-m mark at a normal walking speed, turned, walked back to the chair, and sat down with their back against the chair. Timing began on the “go” command and stopped when the participant’s back contacted the chair back on return. Shorter TUG times indicate better knee activity. The TUG was administered at the baseline (week 0), week 6 and week 12.

Angle Change in the Range of Motion (ROM)

Knee ROM of flexion was measured by a professional physical therapist using a knee goniometer. Participants were positioned supine on the examination table for flexion measurements. Bone landmarks were identified: the lateral femoral epicondyle (axis), the greater trochanter (proximal reference), and the lateral malleolus (distal reference). The active ROM (AROM) was measured as a participant actively bent their knee to the largest angle; passive ROM (PROM) was measured when the examiner moved the calf to the end, as the subject felt only minimal pain with consistent, gentle overpressure when indicated. The knee ROM was assessed at the baseline (week 0), week 6, and week 12.

Point Changes in the Western Ontario and McMaster Universities Arthritis Index (WOMAC)

The WOMAC is a questionnaire used by health professionals to assess knee and hip OA, that comprises three dimensions: pain (5 items), stiffness (2 items), and physical function (17 items). The version used in this study had a Likert format (0 = none to 4 = extreme), yielding subscale raw score ranges of 0–20 for pain, 0–8 for stiffness, 0–68 for physical function, and a total score range of 0–96, with higher scores indicating worse joint severity. The WOMAC score was administered at the baseline (week 0), week 6, and week 12.

Inflammation Marker

Tumor necrosis factor (TNF)- α was used as an indicator of inflammation. Concentrations of TNF- α were determined with a human enzyme-linked immunosorbent assay (ELISA) kit (catalog no. SSTA00E, R&D Systems (Bio-Techne), America).

Compliance

Participants received a record book to log their daily capsule intake and were instructed to return the empty containers at weeks 6 and 12, at which point the researcher counted the remaining capsules. The formula for compliance was as follows: (number of doses taken \div number of doses prescribed) \times 100%.

Statistical analysis

Values are displayed as the mean \pm standard deviation (SD). IBM SPSS Statistics (Version 18) was used for data analyses. An independent t-test was used to compare basic data during the same period. A one-tailed paired t-test was used to compare changes in placebo and test groups in week 0 vs. week 6, week 6 vs. week 12, and week 0 vs. week 12. A p value of < 0.05 indicated a significant difference.

Results

Participant Characteristics

Thirty-two adults (age range, 20–67 years) were enrolled in the study. Two participants withdrew for personal reasons before week 6, resulting in 30 participants who completed the trial through the final assessment. Ages in the placebo and test groups were 33.80 ± 16.65 and 34.80 ± 16.45 years, respectively; the difference was not statistically significant between the two groups ($p=0.870$) (Table 1). Overall, participant adherence was high, with mean

compliance rates of 94.47% through week 6 and 95.08% at week 12, showing no significant difference in compliance between any time spot.

Table 1: Characteristics of enrolled subjects.

	All subject (N=30)	Placebo (N=15)	Test (N=15)	p
Male	9	5	4	
Female	21	10	11	
Age (years)				
20~30	20	10	10	
31~40	1	1	0	
41~50	1	0	1	
51~60	3	3	3	
61~70	2	1	1	
Mean \pm SD	34.30 \pm 16.27	33.80 \pm 16.65	34.80 \pm 16.45	0.870
All values are the mean \pm standard deviation.				
p values between the placebo and test groups were evaluated using a paired t-test, and $p < 0.05$ indicated a significant difference.				

Knee Joint Pain Assessment

Both groups demonstrated reductions in pain scores over the study period. In the normal walk item, the placebo group showed a significant decrease in left-leg pain at week 12 compared to the baseline (week 0), and a significant decrease in right-leg pain at week 12 compared to both weeks 0 and 6. In the test group, pain in both legs at week 12 was significantly lower than that at weeks 0 and 6. In the stand up/squat down tests, pain scores significantly decreased over time in both groups; additionally, in the test group, left-leg pain showed a significant decrease across all three time points. In the bend-to-the-largest-angle evaluation, both the placebo and test groups exhibited significant reductions in pain at week 12 relative to the baseline (Table 2).

Table 2: Change in scores on the visual analog scale for pain.

	Placebo (N=15)		Test (N=15)	
	Δ	p value	Δ	p value
Normal walk, left knee				
Week 0 vs. 6	-0.34 \pm 0.90	0.083	-0.01 \pm 1.11	0.482
Week 6 vs. 12	-0.30 \pm 0.69	0.057	-0.64 \pm 0.62	0.001*
Week 0 vs. 12	-0.64 \pm 1.16	0.026*	-0.65 \pm 0.71	0.002*
Normal walk, right knee				
Week 0 vs. 6	-0.20 \pm 1.16	0.257	0.15 \pm 1.00	0.283
Week 6 vs. 12	-0.45 \pm 0.83	0.027*	-0.67 \pm 0.68	0.001*
Week 0 vs. 12	-0.65 \pm 1.14	0.022*	-0.52 \pm 0.79	0.012*
Stand up/squat down, left knee				
Week 0 vs. 6	-1.02 \pm 1.19	0.003*	-0.85 \pm 1.75	0.040*
Week 6 vs. 12	-0.52 \pm 1.16	0.053	-0.71 \pm 0.93	0.005*
Week 0 vs. 12	-1.54 \pm 1.54	0.001*	-1.56 \pm 1.42	$< 0.001^*$
Stand up/squat down, right knee				
Week 0 vs. 6	-0.79 \pm 1.17	0.010*	-0.75 \pm 1.67	0.053
Week 6 vs. 12	-0.53 \pm 1.08	0.038*	-0.58 \pm 0.87	0.011*
Week 0 vs. 12	-1.33 \pm 1.62	0.003*	-1.33 \pm 1.43	0.001*
Bend to the largest angle, left knee				
Week 0 vs. 6	-0.99 \pm 1.27	0.005*	-0.27 \pm 1.22	0.206
Week 6 vs. 12	-0.56 \pm 0.81	0.009*	-0.71 \pm 1.31	0.027*

Week 0 vs. 12	-1.55±1.61	0.001*	-0.98±1.20	0.003*
Bend to the largest angle, right knee				
Week 0 vs. 6	-0.89±1.28	0.009*	-0.07±1.34	0.425
Week 6 vs. 12	-0.65±0.91	0.008*	-0.91±1.52	0.018*
Week 0 vs. 12	-1.53±1.61	0.001*	-0.98±1.20	0.003*
Values are the mean±standard deviation.				
*Statistically significant difference ($p < 0.05$, by a one-tailed paired t -test).				

Knee Joint Activity Assessment

The TUG results demonstrated a significant time-dependent improvement in the test group across the three assessment points, whereas the placebo group showed a significant improvement only at week 6 that was attenuated by week 12 (Table 3).

Table 3: Time change in the timed up-and-go test.

	Placebo (N=15)		Test (N=15)	
	Δ	p value	Δ	p value
Week 0 vs. 6	-1.23±1.12	<0.001*	-0.48±1.00	0.043*
Week 6 vs. 12	-0.11±0.68	0.272	-0.27±0.59	0.047*
Week 0 vs. 12	-1.33±1.63	0.004*	-0.75±1.00	0.006*
Values are the mean±standard deviation.				
*Statistically significant difference ($p < 0.05$, by a one-tailed paired t -test).				

Knee Joint Mobility Assessment

Knee joint mobility was assessed by AROM and PROM. In the test group, AROM and PROM of the left knee and PROM of the right knee had significantly increased by week 6 compared to the baseline, indicating early improvement in knee mobility. By contrast, the placebo group exhibited a significant decline in left-knee AROM at week 12 relative to earlier time points. Moreover, in the test group, both left-knee AROM and PROM at week 12 were significantly reduced compared to week 6 (Table 4).

Table 4: Angle change in range of motion (ROM).

	Placebo (N=15)		Test (N=15)	
	Δ	p value	Δ	p value
AROM, left knee				
Week 0 vs. 6	-0.53±5.48	0.36	3.13±5.59	0.02*
Week 6 vs. 12	-3.27±6.28	0.03*	-4.00±6.04	0.01*
Week 0 vs. 12	-3.80±6.42	0.02*	-0.87±10.05	0.37
AROM, right knee				
Week 0 vs. 6	-0.40±5.70	0.39	2.67±5.97	0.05
Week 6 vs. 12	-2.80±6.09	0.05	-2.00±5.55	0.38
Week 0 vs. 12	-3.20±7.29	0.06	0.67±8.41	0.09
PROM, left knee				
Week 0 vs. 6	-0.13±4.87	0.46	3.33±5.11	0.01*
Week 6 vs. 12	-1.67±5.60	0.13	-3.87±6.12	0.01*
Week 0 vs. 12	-1.80±5.35	0.11	-0.53±9.81	0.42
PROM, right knee				
Week 0 vs. 6	0.27±5.28	0.42	2.93±6.09	0.04*
Week 6 vs. 12	-1.07±6.67	0.27	-2.53±5.42	0.05
Week 0 vs. 12	-0.80±7.66	0.35	0.40±8.53	0.43
Values are the mean±standard deviation.				

* Statistically significant difference ($p < 0.05$, by a one-tailed paired t -test).
AROM, active ROM; PROM, passive ROM.

Inflammation Marker

Serum TNF- α concentrations significantly decreased from the baseline to week 6 in both groups. By week 12, the decline in the test group was larger than that in the placebo group (Table 5).

Table 5: Changes in an inflammation marker.

	Placebo (N=15)		Test (N=15)	
	Δ	p value	Δ	p value
TNF- α				
Week 0 vs. 6	-0.12±0.16	0.018*	-0.19±0.25	0.01*
Week 6 vs. 12	-0.01±0.13	0.842	0.06±0.29	0.459
Week 0 vs. 12	-0.12±0.23	0.063	-0.14±0.31	0.112
Values are the mean±standard deviation.				
TNF- α , tumor necrosis factor alpha.				

Knee Pain Severity Assessment

Knee pain severity was evaluated using the WOMAC questionnaire. In the test group, both pain and physical function subscale scores showed significant reductions at week 12 compared to the baseline and week 6. In the placebo group, scores for pain, stiffness, and physical function were significantly reduced at week 6; however, these improvements were not sustained to week 12 (Table 6).

Table 6: Change in WOMAC scores.

	Placebo (N=15)		Test (N=15)	
	Δ	p value	Δ	p value
Pain				
Week 0 vs. 6	-1.27±1.90	0.011*	-0.53±2.50	0.212
Week 6 vs. 12	-4.0±1.40	0.144	-1.07±1.83	0.020*
Week 0 vs. 12	-1.67±2.92	0.022*	-1.60±3.11	0.033*
Stiffness				
Week 0 vs. 6	-0.80±1.08	0.006*	-0.07±1.03	0.403
Week 6 vs. 12	0.13±0.83	0.273	-0.20±0.56	0.094
Week 0 vs. 12	-0.67±1.05	0.014*	-0.27±1.16	0.195
Physical function				
Week 0 vs. 6	-3.53±3.76	0.001*	-2.47±5.87	0.063
Week 6 vs. 12	0.27±3.56	0.388	-1.67±3.52	0.044*
Week 0 vs. 12	-3.27±4.73	0.009*	-4.13±7.52	0.026*
Values are the mean±standard deviation.				
* Statistically significant difference ($p < 0.05$, by a one-tailed paired t -test).				
WOMAC, Western Ontario and McMaster Universities Arthritis Index.				

Discussion

This study evaluated the effects of daily ingestion of two capsules of VITABOX® U.S. patented UC-II®+high-efficiency glucosamine+C3 super curcumin a day for 12 weeks in adults with knee pain. Results showed that pain levels in both legs of the test group had significantly decreased by week 12, and the WOMAC pain subscale score had decreased, indicating improved symptom burden. For knee joint function, both groups showed significantly

decreased times of the TUG test, and significantly increased knee ROM in week 6, and also the WOMAC physical function subscale score had decreased.

According to James et al., after using 40 mg UC-II per day, WOMAC scores decreased after 6 months, which were the same results as this study [17]. In addition, a meta-analysis by Liu et al. indicated that UC-II can significantly alleviate knee joint pain, which was similar to results of the stand up/squat down and bend to the largest angle evaluations using a VAS [18]. In addition to UC-II, curcumin also proved to have an anti-inflammatory effect. Clinical research by Henrootin et al. showed that after giving 45–80-year-old adults 186.68 or 280.02 mg curcumin extract per day for 3 months, pain VAS scores decreased over time [19].

In this study, we discovered that in the TUG test, the times of both the placebo and test groups decreased, indicating that the participants' walking function improved in both groups, and the effect on the test group lasted until week 12. This result was also similar to that of the study of Adrian et al. after administering 1000 mg curcumin extract per day for 8 weeks, times of the TUG test significantly decreased [20].

TNF- α is a cytokine commonly used to evaluate the inflammatory condition in the human body. After articular cartilage is worn and causes synovial inflammation, it will secrete proinflammatory cytokines, such as activated macrophages which produce the TNF- α proinflammatory factor [21,22], and it stimulates chondrocytes to produce prostaglandin E2 and nitric oxide, which may exacerbate local inflammation and pain intensity and are related to chondrocyte degeneration. Hsueh et al. demonstrated that curcumin could lower the TNF- α in OA patients, but more research is needed to confirm the influence of TNF- α on OA [23].

In this study, we discovered that the test group exhibited increased AROM and PROM by week 6. UC-II can increase knee ROM in healthy adults with knee discomfort [24]; Liu et al. demonstrated that curcumin decreased inflammation and increased the angle of knee ROM and knee joint function [25]. The reasons why the expression only significantly increased by week 6 but was not sustained to week 12 might be that first was a change in the weather. According to Elena et al.'s research, weather and time change may influence ROM measurements [26] and in this study, the season of week 0 was summer, and week 12 was winter, so the result may have been affected by weather change, the clothes of participants, and the knee joint status on the measurement day. A second possible reason is the thickness of calf muscles; due to various body types; a subject's calf muscles being larger or tighter can lead to errors in knee ROM measurements.

The anti-inflammatory mechanism of UC-II occurs through oral intake; the antigen of UC-II interacts with Peyer's patch in lymphoid tissues of the small intestine, and activates the production of regulatory T cells, that inhibit immune cell overactivation to alleviate OA symptoms [27]. Rong et al. also showed that UC-II could increase the secretion of anti-inflammation cytokines

interleukin (IL)-10 and transforming growth factor (TGF)- β in an OA rat model [28], indicating that it may improve knee joint inflammation through the effect of regulatory T cells on immune cell inhibition and promote anti-inflammatory cytokine secretion. Results of this study showed that both groups that received UC-II showed improvements in knee joint function through the VAS, TUG test, and WOMAC.

Previous studies demonstrated that glucosamine exerts anti-inflammatory effects, modulating markers such as nitric oxide, cyclooxygenase(COX)-2, and IL-6 [29]. Amanetal. reported that both chondroitin sulfate/glucosamine and curcumagalactomannoside/glucosamine combinations improved knee function after 84 days; However, the curcumagalactomannoside/glucosamine group achieved greater reductions in pain and stiffness and superior improvements in patients' physical function compared to the other group, a difference the authors attributed to the stronger anti-inflammatory activity of curcumin [30].

Curcumin, an active component derived from *Curcuma longa*, has demonstrated both antioxidant and anti-inflammatory effects [31]. Its antioxidant activity is mediated by upregulation of antioxidant enzyme expressions and direct scavenging of free radicals, while its anti-inflammatory actions involve inhibition of signaling pathways such as nuclear factor (NF)- κ B, toll-like receptor 4 (TLR4), and myeloid differentiation primary response 88 (MyD88) [32,33]. Suppression of these pathways subsequently reduces production of proinflammatory cytokines, including TNF- α [34].

As to the strengths and limitations of this article, this is the first article to research the effect of the combination of UC-II, glucosamine, and curcumin on improving knee pain. Limitations include the small sample size and short study duration: we analyzed 30 participants, with 15 participants in each group, and conducted the research over 12 weeks. In the future, experiments with a longer intervention time should be undertaken to explore the effects of long-term use of the combination.

Conclusions

After using VITABOX® U.S. patented UC-II®+high-efficiency glucosamine+C3 super curcumin for 12 weeks, the effects of alleviating pain and improving the function of the knee joint were observed.

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