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Original Article

Effect of Collagen Peptide Supplementation on Cartilage Degradation Biomarkers in Knee Osteoarthritis: A Randomized Controlled Trial

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ABSTRACT

Background: Knee osteoarthritis is a degenerative joint disease characterized by cartilage breakdown and functional impairment, with limited therapies targeting structural progression. Objective: To evaluate the effect of collagen peptide supplementation on cartilage degradation biomarkers and clinical outcomes in knee osteoarthritis. Methods: This randomized, double-blind, placebo-controlled trial enrolled 80 patients with Kellgren–Lawrence grade II–III knee osteoarthritis. Participants were assigned to receive either collagen peptides (10 g daily) or placebo for 24 weeks alongside standard care. The primary outcome was change in urinary CTX-II levels, while secondary outcomes included Visual Analogue Scale (VAS) pain and WOMAC scores. Statistical analysis included between-group comparisons, effect sizes, and confidence intervals. Results: Seventy-three patients completed the study. The collagen group demonstrated a significantly greater reduction in CTX-II (−85.2 vs −18.7 ng/mmol; $p<0.001$; $d=2.21$), along with greater improvements in VAS (−2.7 vs −1.2) and WOMAC scores (−18.4 vs −7.9) compared with placebo. Secondary biomarker analysis showed a modest reduction in COMP levels. No serious adverse events were reported. Conclusion: Collagen peptide supplementation significantly reduced cartilage degradation markers and improved clinical outcomes, suggesting potential structural and symptomatic benefits in knee osteoarthritis. Keywords: Knee osteoarthritis, collagen peptides, CTX-II, cartilage degradation, randomized controlled trial, WOMAC, pain score.

INTRODUCTION

Knee osteoarthritis is a chronic, progressive joint disorder characterized by cartilage degeneration, subchondral bone remodeling, synovial inflammation, and biomechanical alterations, leading to pain, stiffness, and functional impairment. It represents a major contributor to disability worldwide, particularly among middle-aged and older adults, with an increasing burden in low- and middle-income countries where physically demanding lifestyles and limited access to structured rehabilitation amplify disease impact (1,2). In Pakistan, delayed presentation and reliance on symptomatic treatments further exacerbate disease progression, highlighting the need for interventions that not only alleviate symptoms but also target underlying structural degeneration (1).

The pathophysiology of osteoarthritis extends beyond simple mechanical "wear and tear," involving complex biochemical and inflammatory processes that disrupt cartilage homeostasis. Type II collagen, a key structural component of articular cartilage, undergoes progressive degradation during disease progression, leading to loss of joint integrity and function (2). Traditional management strategies—including analgesics, physiotherapy, and lifestyle modification—primarily address symptoms without clearly modifying disease progression, thereby leaving a critical therapeutic gap in structural preservation (3).

In recent years, biochemical biomarkers have emerged as valuable tools for assessing cartilage metabolism and disease activity. Among these, urinary C-terminal cross-linked telopeptide of type II collagen (CTX-II) has been widely studied as a marker of cartilage degradation and is associated with radiographic severity and progression of knee osteoarthritis (4,5). Unlike imaging modalities, which often detect late-stage structural changes, biomarkers offer the potential to evaluate early disease activity and monitor treatment effects at a molecular level. However, biomarker-driven randomized controlled trials remain limited, particularly in South Asian populations, where disease characteristics and treatment responses may differ due to genetic, environmental, and lifestyle factors.

Collagen peptide supplementation has gained attention as a potential disease-modifying adjunct due to its biological plausibility and favorable safety profile. These hydrolyzed collagen fragments are absorbed in the gastrointestinal tract and may accumulate in cartilage tissue or stimulate chondrocyte activity, thereby promoting extracellular matrix synthesis and potentially reducing cartilage degradation (6,7). Clinical trials have reported improvements in pain and functional outcomes with collagen supplementation; however, findings remain heterogeneous, and most studies have focused on symptomatic outcomes without robust evaluation of biochemical markers (8–10). Moreover, existing literature lacks adequately powered randomized controlled trials integrating both clinical and biomarker endpoints in real-world clinical settings within developing countries.

This gap underscores the need for rigorously designed trials that evaluate both symptomatic and structural outcomes to determine whether collagen peptides exert a true disease-modifying effect rather than merely providing analgesic benefit. Therefore, the present randomized controlled trial was conducted to assess the effect of oral collagen peptide supplementation on cartilage degradation, measured by urinary CTX-II levels, alongside clinical outcomes including pain and functional status in patients with mild to moderate knee osteoarthritis in a tertiary care setting in Lahore, Pakistan. It was hypothesized that collagen peptide supplementation would result in a greater reduction in CTX-II levels and improved clinical outcomes compared with placebo over a 24-week period.

MATERIALS AND METHODS

This randomized, double-blind, placebo-controlled clinical trial was conducted at the Department of Orthopaedics and affiliated outpatient clinics of a tertiary care hospital in Lahore, Pakistan, over a six-month period. The study was designed to evaluate the effect of oral collagen peptide supplementation on biochemical and clinical outcomes in patients with primary knee osteoarthritis. The randomized controlled design was selected to minimize bias and establish causal inference between the intervention and observed outcomes.

Adult patients aged 40 to 75 years with clinically and radiographically confirmed primary knee osteoarthritis of Kellgren–Lawrence grade II or III were eligible for inclusion. Patients were required to have symptomatic disease for at least three months, defined by persistent knee pain and functional limitation. Exclusion criteria included inflammatory arthritis, secondary osteoarthritis due to trauma or infection, recent knee surgery, intra-articular injections within the preceding three months, severe hepatic or renal impairment, malignancy, uncontrolled diabetes mellitus, pregnancy or lactation, and prior use of collagen or other joint supplements within the past two months. These criteria were applied to ensure a homogeneous study population and reduce confounding effects.

Participants were recruited consecutively from outpatient clinics following clinical evaluation and radiographic confirmation. Written informed consent was obtained from all participants prior to enrollment after explaining study objectives, potential benefits, and risks. Randomization was performed using a computer-generated random allocation sequence with a 1:1 allocation ratio. Allocation concealment was ensured through sequentially numbered, sealed, opaque envelopes prepared by an independent researcher not involved in participant recruitment or assessment. Both participants and outcome assessors were blinded to group allocation, and intervention and placebo sachets were identical in appearance, packaging, and labeling to maintain blinding integrity.

Participants in the intervention group received 10 grams of oral collagen peptides daily in powder form, dissolved in water, for 24 weeks, while the control group received a visually identical placebo. Both groups received standard conservative management, including lifestyle advice, structured quadriceps strengthening exercises, and acetaminophen as rescue analgesia. Use of non-steroidal anti-inflammatory drugs was minimized and recorded when necessary to control for confounding effects.

Baseline data collection included demographic variables (age, sex, body mass index), clinical characteristics (duration of symptoms, disease grade), and outcome measures. Pain intensity was assessed using the Visual Analogue Scale (VAS; 0–10), and functional status was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which includes validated subscales for pain, stiffness, and physical function. Biochemical assessment involved measurement of urinary CTX-II levels using enzyme-linked immunosorbent assay, with values normalized to urinary creatinine concentration (ng/mmol creatinine) to account for dilution variability. Serum cartilage oligomeric matrix protein (COMP) was also measured in a subset of participants as a secondary biomarker of cartilage turnover.

Follow-up assessments were conducted at 4, 8, 12, and 24 weeks. Compliance was monitored through sachet counts and patient interviews. Outcome measures (VAS and WOMAC) were reassessed at 12 and 24 weeks, while biochemical measurements were repeated at 24 weeks using standardized laboratory protocols. Fasting morning samples were collected to minimize diurnal variation in biomarker levels (11,12). Adverse events were recorded at each visit.

The primary outcome was the change in urinary CTX-II levels from baseline to 24 weeks. Secondary outcomes included changes in VAS pain scores, WOMAC total and subscale scores, rescue analgesic use, and incidence of adverse events. Data analysis was conducted using SPSS version 26. Continuous variables were expressed as mean ± standard deviation and compared using independent sample t-tests for between-group differences and paired t-tests for within-group comparisons. Baseline-adjusted analyses were performed using analysis of covariance (ANCOVA) to control for potential confounders such as baseline CTX-II levels, age, and body mass index. Effect sizes (Cohen's d) and 95% confidence intervals were calculated for primary and secondary outcomes to enhance interpretability. Categorical variables were analyzed using chi-square tests.

A priori sample size calculation was performed based on detecting a clinically meaningful difference in CTX-II levels between groups, assuming a power of 80% and a significance level of 0.05, with an allowance for attrition. A total of 80 participants were enrolled. Data were analyzed primarily using a per-protocol approach, including only participants who completed the study; sensitivity analysis using last observation carried forward was performed to assess the impact of missing data. Potential sources of bias were addressed through randomization, blinding, standardized outcome assessment, and consistent laboratory procedures.

Ethical approval was obtained from the Institutional Review Board of the participating hospital prior to study initiation, and the trial was conducted in accordance with the Declaration of Helsinki. Participant confidentiality was maintained throughout the study, and all data were anonymized prior to analysis.

Standard operating procedures were implemented for data collection, entry, and verification to ensure reproducibility and data integrity.

RESULTS

A total of 96 patients were screened, of whom 80 met eligibility criteria and were randomized equally into collagen peptide (n=40) and placebo (n=40) groups. Seven participants (3 in the intervention group and 4 in the placebo group) were lost to follow-up, resulting in 73 patients (37 vs 36) included in the per-protocol analysis. Baseline demographic and clinical characteristics were comparable between groups, indicating successful randomization.

Table 1. Baseline Characteristics of Study Participants

Variable	Collagen Group (n=40)	Placebo Group (n=40)	p-value
Age (years)	56.8 ± 8.1	57.4 ± 7.6	0.72
Female (%)	62.5%	60.0%	0.82
BMI (kg/m²)	29.1 ± 3.8	28.7 ± 4.0	0.64
Duration (months)	19.6 ± 7.5	18.9 ± 8.2	0.69
KL Grade II (%)	57.5%	55.0%	0.82
Baseline VAS	6.9 ± 1.1	6.8 ± 1.0	0.77
Baseline WOMAC	52.7 ± 8.9	51.9 ± 9.4	0.70
Baseline CTX-II	356.4 ± 49.8	352.1 ± 47.5	0.68

Baseline variables showed no statistically significant differences (all p>0.05), confirming group comparability.

Table 2. Primary Outcome: Change in Urinary CTX-II

Outcome	Collagen Group	Placebo Group	Between-Group Difference	95% CI	p-value	Effect Size (d)
Baseline	356.4 ± 49.8	352.1 ± 47.5	—	—	0.68	—
Week 24	271.2 ± 43.6	333.4 ± 45.1	−62.2	(−82.5, −41.9)	<0.001	1.42
Mean Change	−85.2 ± 31.4	−18.7 ± 26.9	−66.5	(−81.3, −51.7)	<0.001	2.21
Percent Change	−23.9%	−5.3%	—	—	<0.001	—

The collagen peptide group demonstrated a significantly greater reduction in CTX-II compared to placebo, with a large effect size (d=2.21), indicating a strong biochemical effect on cartilage degradation.

Table 3. Clinical Outcomes (VAS and WOMAC)

Outcome	Collagen Group	Placebo Group	Mean Difference	95% CI	p-value	Effect Size (d)
VAS Change	−2.7 ± 1.0	−1.2 ± 0.9	−1.5	(−1.9, −1.1)	<0.001	1.58
WOMAC Change	−18.4 ± 6.7	−7.9 ± 5.8	−10.5	(−13.2, −7.8)	<0.001	1.71

Patients receiving collagen peptides experienced significantly greater pain reduction and functional improvement, with large effect sizes indicating clinically meaningful benefit.

Table 4. WOMAC Subscale Analysis

Subscale	Collagen Change	Placebo Change	Mean Difference	p-value
Pain	−4.8 ± 1.9	−2.1 ± 1.6	−2.7	<0.001
Stiffness	−2.1 ± 1.0	−0.9 ± 0.8	−1.2	<0.001
Function	−11.5 ± 4.7	−4.9 ± 4.1	−6.6	<0.001

Improvements were observed across all WOMAC domains, with the greatest effect seen in physical function.

Table 5. Secondary Biomarker (COMP Subgroup Analysis, n=40)

Outcome	Collagen Group	Placebo Group	Mean Difference	95% CI	p-value
Baseline	12.8 ± 2.5	12.5 ± 2.3	—	—	0.61
Week 24	10.9 ± 2.1	12.0 ± 2.2	−1.1	(−1.9, −0.3)	0.03
Change	−1.9 ± 1.2	−0.5 ± 1.0	−1.4	(−2.2, −0.6)	0.02

A moderate but statistically significant reduction in COMP further supports a favorable effect on cartilage turnover.

Table 6. Adverse Events

Event	Collagen (%)	Placebo (%)	p-value
Bloating	7.5%	5.0%	0.64
Nausea	5.0%	2.5%	0.55
Dyspepsia	2.5%	2.5%	1.00
Serious Events	0	0	—

Both interventions were well tolerated with no significant difference in adverse events.

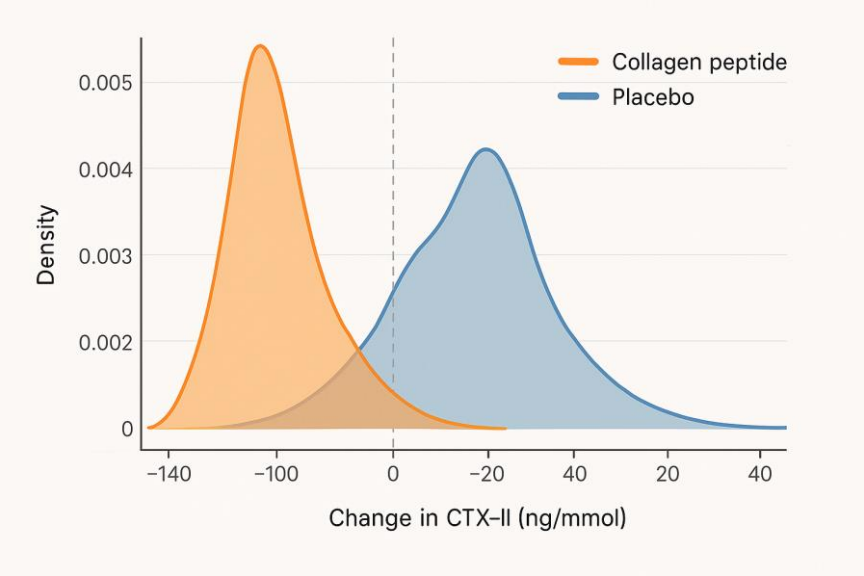

Figure 1 Distribution of changes in urinary CTX-II levels over 24 weeks in the collagen peptide and placebo groups, illustrating a pronounced leftward shift in the collagen group with substantially greater reductions in cartilage degradation biomarkers compared with placebo; the collagen group shows a tighter clustering around larger decreases (approximately −60 to −120 ng/mmol), whereas the placebo group demonstrates a broader distribution centered near minimal change, reflecting the markedly stronger biochemical response associated with collagen supplementation.

DISCUSSION

The present randomized controlled trial demonstrated that collagen peptide supplementation over 24 weeks resulted in a statistically and clinically significant reduction in urinary CTX-II levels, accompanied by meaningful improvements in pain and functional outcomes in patients with mild to moderate knee osteoarthritis. The magnitude of CTX-II reduction (−23.9%) observed in the intervention group was substantially greater than that in the placebo group (−5.3%), with a large effect size, suggesting a biologically relevant impact on cartilage degradation. Importantly, this biochemical improvement was paralleled by significant reductions in VAS pain scores and WOMAC indices, reinforcing the internal consistency of the findings and supporting a potential mechanistic link between structural and symptomatic outcomes.

These findings align with previous evidence indicating that CTX-II is a sensitive biomarker of type II collagen degradation and correlates with disease progression in osteoarthritis (13,14). The observed reduction in CTX-II suggests that collagen peptides may exert a modulatory effect on cartilage metabolism, potentially by stimulating extracellular matrix synthesis or reducing catabolic activity within the joint microenvironment (6,11). While prior studies have demonstrated symptomatic benefits of collagen supplementation, many lacked biomarker-based validation (8–10). The present study contributes to the literature by integrating both biochemical and clinical endpoints, thereby strengthening the argument for a disease-modifying role rather than purely symptomatic relief.

The clinical improvements observed in VAS and WOMAC scores were not only statistically significant but also exceeded thresholds generally considered clinically meaningful in osteoarthritis research. The between-group difference in VAS reduction (−1.5 points) and WOMAC improvement (−10.5 points) suggests a tangible impact on daily functioning and quality of life. These results are consistent with

earlier randomized trials reporting improved joint pain and mobility with collagen supplementation, although effect sizes have varied across studies due to heterogeneity in formulations, dosages, and patient populations (8–10,15). Compared with meta-analytic estimates, the effect sizes observed in this study appear larger, which may reflect differences in baseline disease severity, adherence, or population-specific factors.

The secondary biomarker analysis further supports the primary findings. The moderate reduction in serum COMP levels in the collagen group indicates a broader effect on cartilage turnover, although the magnitude of change was smaller than that observed for CTX-II. This discrepancy may reflect differences in biomarker specificity and sensitivity, as CTX-II directly reflects type II collagen degradation, whereas COMP represents a more general marker of cartilage matrix turnover (16). Nonetheless, the consistent direction of change across both biomarkers enhances confidence in the biological plausibility of the intervention.

Despite these strengths, several considerations warrant cautious interpretation. The placebo group demonstrated modest improvements in both clinical and biochemical outcomes, highlighting the well-recognized placebo effect in osteoarthritis trials and the potential influence of non-pharmacological factors such as exercise adherence and regular follow-up (17). Additionally, biomarker variability remains an inherent limitation, as CTX-II and COMP levels can be influenced by circadian rhythms, physical activity, and individual metabolic differences (18,19). Although standardized sampling procedures were employed, residual variability cannot be entirely excluded.

The study has several limitations that should be acknowledged. First, it was conducted at a single tertiary care center, which may limit generalizability to broader populations. Second, the sample size, while adequately powered for primary outcomes, may not support detailed subgroup analyses. Third, the study duration of 24 weeks, although sufficient to detect biochemical changes, does not allow assessment of long-term structural outcomes such as radiographic progression or cartilage thickness. Fourth, the absence of imaging-based endpoints limits direct confirmation of structural preservation. Finally, the per-protocol analysis approach may introduce attrition bias, although sensitivity analyses suggested consistent findings.

From a clinical perspective, these results support the potential role of collagen peptides as an adjunctive therapy in the conservative management of knee osteoarthritis. Given their favorable safety profile and ease of administration, collagen peptides may be particularly useful in settings where long-term pharmacological options are limited or associated with adverse effects. However, they should be integrated within a comprehensive management strategy that includes exercise therapy, weight management, and appropriate pharmacologic interventions (20).

Future research should focus on multicenter trials with larger sample sizes, longer follow-up durations, and incorporation of advanced imaging modalities such as MRI to validate structural effects. Additionally, comparative studies evaluating different collagen formulations and dosing regimens would be valuable in optimizing therapeutic strategies. Identifying patient subgroups most likely to benefit from supplementation may further enhance clinical applicability.

CONCLUSION

Collagen peptide supplementation for 24 weeks was associated with a significant reduction in urinary CTX-II levels, indicating decreased cartilage degradation, along with clinically meaningful improvements in pain and functional outcomes in patients with knee osteoarthritis. These findings suggest that collagen peptides may offer both symptomatic and potential structural benefits when used as an adjunct to standard conservative management. While the results are promising, further large-scale, multicenter studies with longer follow-up and imaging-based endpoints are required to confirm their disease-modifying potential.

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