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A Randomized Trial of Collagen Peptides Combined with Resistance Training for Pain and Cartilage Turnover in Knee Osteoarthritis

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ABSTRACT

Background: Knee osteoarthritis causes chronic pain and functional limitation, and while resistance training improves symptoms, its influence on cartilage metabolism is uncertain. Collagen peptide supplementation may support connective tissue health, but evidence for combined use with exercise remains limited. Objective: To determine whether collagen peptide supplementation combined with supervised resistance training improves pain and serum biomarkers of cartilage metabolism compared with resistance training alone in adults with mild to moderate knee osteoarthritis. Methods: In this 12-week parallel-group randomized controlled trial conducted in South Punjab, 120 participants were randomized (1:1) to collagen peptides plus resistance training or resistance training alone. Pain intensity was assessed at baseline and 12 weeks using a knee-specific pain rating scale. Serum biomarkers representing cartilage degradation and synthesis were assessed at baseline and follow-up and expressed as percentage change. Between-group differences were evaluated using independent sample tests, with effect sizes and 95% confidence intervals reported. Results: Of 120 randomized participants, 114 completed follow-up. Pain decreased in both groups, with greater improvement in the combined group (12-week pain: 3.2 ± 0.9 vs 4.5 ± 1.0; mean difference −1.30, 95% CI −1.64 to −0.96; $p < 0.001$). Cartilage degradation biomarkers decreased more in the combined group (−22.4 ± 6.8% vs −10.1 ± 5.9%; $p < 0.001$), and synthesis biomarkers increased more (+18.6 ± 5.2% vs +7.9 ± 4.8%; $p < 0.001$). No adverse events were reported. Conclusion: Collagen peptides combined with resistance training produced superior short-term improvements in pain and cartilage turnover biomarkers compared with resistance training alone.

Keywords
Knee osteoarthritis; collagen peptides; resistance training; pain; cartilage turnover; serum biomarkers.

INTRODUCTION

Knee osteoarthritis is a highly prevalent degenerative joint disorder and a major contributor to chronic pain, mobility limitation, and disability in middle-aged and older adults, with increasing population-level burden due to aging and rising obesity rates (1). The condition is characterized by progressive degradation of articular cartilage, remodeling of subchondral bone, and a chronic low-grade inflammatory milieu, collectively leading to pain sensitization, impaired function, and gradual loss of joint integrity (2). Although pharmacological therapies such as non-steroidal anti-inflammatory drugs and analgesics remain widely used for symptom relief, they carry well-established risks with long-term use and do not meaningfully alter underlying disease progression (3). Surgical options are typically reserved for advanced disease and may not be acceptable or accessible to many patients, reinforcing the importance of safe, scalable, and conservative interventions that address both symptomatic and biological dimensions of knee osteoarthritis (4).

Current management paradigms emphasize non-pharmacological approaches as the foundation of care, with structured exercise therapy consistently recommended as a first-line strategy (5). Within this context, resistance training has emerged as a cornerstone intervention because it enhances quadriceps strength, improves neuromuscular control, and stabilizes the knee joint, thereby reducing mechanical stress and improving pain and physical function (6). Beyond these mechanical effects, resistance training may influence inflammatory and metabolic pathways and improve cartilage nutrition through cyclic joint loading, providing a plausible biological basis for beneficial joint-tissue adaptation (7). Nevertheless, while resistance training reliably improves symptoms, its capacity to modify cartilage metabolism or slow structural deterioration remains limited and inconsistent across studies, leaving a persistent gap in conservative osteoarthritis management (8).

This unmet need has driven increasing interest in adjunctive nutritional strategies that may complement exercise and support connective tissue health, particularly collagen peptide supplementation (9). Collagen is a fundamental structural component of articular cartilage, tendons, and ligaments, and cartilage collagen breakdown is central to osteoarthritis pathology. Orally administered collagen peptides are proposed to provide bioactive amino acids and peptides that may stimulate chondrocyte activity, enhance extracellular matrix synthesis, and attenuate cartilage degradation, potentially translating into improvements in pain and joint function (10). However, existing evidence remains heterogeneous, with variable findings and limited mechanistic integration, particularly regarding objective biological markers and clinically meaningful symptom change (11).

A strong scientific rationale supports combining collagen peptides with resistance training, as mechanical loading is a key stimulus for cartilage metabolism, and targeted substrate availability during an anabolic demand state may augment tissue repair or remodeling responses (12). This

synergistic hypothesis is clinically relevant because resistance training may prime joint tissues for adaptive change, while collagen peptides may facilitate structural protein synthesis, potentially shifting cartilage turnover toward a more favorable metabolic balance (13). Despite this plausibility, relatively few randomized trials have directly evaluated the combined effects of collagen peptides and supervised resistance training in knee osteoarthritis while simultaneously measuring patient-centered outcomes such as pain alongside objective biomarkers of cartilage metabolism, limiting the ability to link symptom improvement with biological change (14).

Serum biomarkers of cartilage turnover offer a valuable adjunct to clinical outcomes because they can reflect dynamic processes of cartilage degradation and synthesis that may respond earlier than structural imaging findings. Although biomarkers cannot substitute for imaging-based structural endpoints, they provide mechanistic insight into whether conservative interventions may influence tissue-level pathways relevant to disease progression (15). Integrating biomarker outcomes with pain trajectories can therefore strengthen clinical interpretation and improve translational relevance, particularly when evaluating multimodal interventions that aim to address both symptoms and joint biology (16). Evidence remains limited from underrepresented settings, and generating rigorous randomized data in diverse populations is important for improving external validity and informing real-world conservative care strategies (17).

Accordingly, this randomized controlled trial evaluated whether collagen peptide supplementation combined with supervised resistance training produces greater improvements in knee pain and more favorable changes in serum biomarkers of cartilage metabolism than resistance training alone in adults with mild to moderate knee osteoarthritis. It was hypothesized that the combined intervention would yield superior pain reduction and a larger shift toward reduced cartilage degradation and enhanced cartilage synthesis compared with resistance training alone.

MATERIALS AND METHODS

This parallel-group randomized controlled trial was conducted in outpatient orthopedic and rehabilitation settings in South Punjab, Pakistan, over a 12-week intervention period. Adults aged 40–70 years with a clinical diagnosis of primary knee osteoarthritis and radiographic severity consistent with mild to moderate disease were recruited through clinician referral and community-based screening. Eligibility required knee pain persisting for at least three months and the ability to participate safely in supervised resistance training. Individuals were excluded if they had secondary osteoarthritis, inflammatory arthropathies, recent knee surgery, intra-articular injections within the preceding six months, severe cardiovascular, neurological, renal, or hepatic disorders, current use of collagen supplements or similar nutraceutical interventions, or contraindications to exercise participation. Written informed consent was obtained from all participants prior to enrollment, and confidentiality was maintained throughout the study.

A priori sample size estimation was performed to detect a clinically meaningful between-group difference in pain change over time with 80% power and a two-sided alpha of 0.05, assuming a moderate standardized effect and permitting attrition. A total of 120 participants were recruited and randomized in a 1:1 ratio to a combined intervention group or a resistance training–only control group. Randomization was performed using a computer-generated sequence with allocation concealment implemented via sequentially numbered, opaque, sealed envelopes prepared by personnel not involved in recruitment or outcome assessment. Participants were enrolled by study staff and allocated according to the next available envelope to ensure concealment integrity.

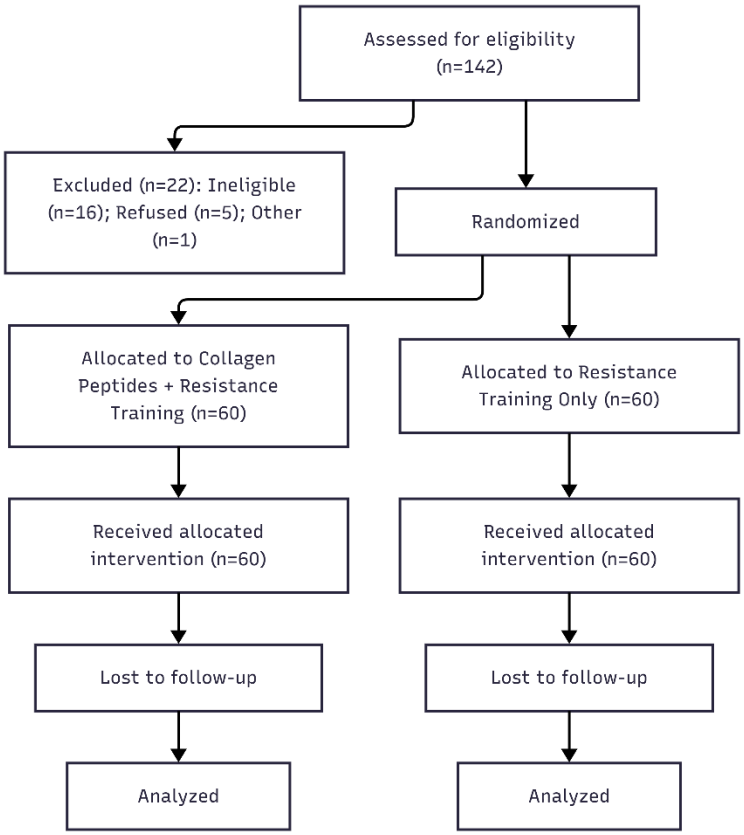

Figure 1 CONSORT Flowchart

Both groups participated in a supervised progressive resistance training program delivered three sessions per week over 12 weeks, targeting major lower-limb muscle groups relevant to knee joint stability. Each session included warm-up activity, structured strengthening exercises, and cool-

down. Training progression was implemented by systematically increasing resistance and/or repetitions across the intervention period according to participant tolerance and standardized progression rules. Attendance was recorded at each session, and adherence was calculated as the percentage of completed sessions relative to the scheduled number. Safety monitoring was performed throughout the program, and participants were instructed to report musculoskeletal discomfort, dizziness, or any other symptoms during or after exercise.

In addition to resistance training, participants in the combined intervention group received oral collagen peptide supplementation once daily throughout the 12-week period, administered as a powder dissolved in water. Participants in the control group received no supplement. Supplement adherence was monitored by weekly self-report and return checks of used containers, and all participants were instructed to maintain their habitual diet and medication regimens during the trial to minimize nutritional confounding.

The primary clinical outcome was pain intensity measured at baseline and at 12 weeks using a standardized knee-specific pain rating scale, with higher values indicating greater pain severity. Secondary outcomes were serum biomarkers of cartilage metabolism representing cartilage degradation and cartilage synthesis. Fasting venous blood samples were collected at baseline and at 12 weeks under standardized conditions. Samples were processed and stored according to laboratory protocols, and biomarker assays were performed using manufacturer-recommended procedures. Biomarker outcomes were expressed as percentage change from baseline to 12 weeks to facilitate interpretation of directional cartilage turnover shifts across participants.

Statistical analyses were performed using standard statistical software. Continuous variables were summarized as mean ± standard deviation and categorical variables as frequency and percentage. Normality assumptions were verified prior to inferential testing. Baseline comparability between groups was evaluated using independent samples t-tests for continuous variables and chi-square tests for categorical variables. Within-group changes from baseline to 12 weeks were evaluated using paired samples t-tests. Between-group differences at 12 weeks and between-group differences in biomarker percentage changes were evaluated using independent samples t-tests. To improve clinical interpretability, between-group mean differences were reported with 95% confidence intervals and standardized effect sizes (Cohen's d). A two-sided p-value < 0.05 was considered statistically significant. Analyses were conducted using the available-case dataset for participants completing follow-up assessments.

RESULTS

A total of 120 participants were enrolled and randomized, with 60 allocated to collagen peptide supplementation plus resistance training and 60 to resistance training alone. Of these, 114 participants completed the 12-week follow-up, yielding a completion rate of 95%. Six participants were lost to follow-up due to personal or logistical reasons unrelated to the intervention. Baseline demographic and clinical characteristics were comparable between groups, with no statistically significant differences observed in age, sex distribution, body mass index, or osteoarthritis duration, supporting successful randomization (Table 1).

At baseline, pain severity was similar between groups (combined group: 6.8 ± 1.1 vs training-only group: 6.7 ± 1.2; $p = 0.637$). After 12 weeks, both groups showed statistically significant within-group reductions in pain; however, the combined group achieved a substantially larger improvement. Mean pain decreased to 3.2 ± 0.9 in the combined group compared with 4.5 ± 1.0 in the training-only group. The between-group difference in pain at 12 weeks was −1.30 points (95% CI: −1.64 to −0.96; $p < 0.001$), representing a large standardized effect size (Cohen's $d = -1.37$) (Table 2). In change-score terms, pain declined by −3.6 points in the combined group versus −2.2 points in the training-only group, indicating a greater symptom reduction associated with collagen supplementation alongside supervised training.

Serum biomarker outcomes demonstrated more favorable cartilage turnover changes in the combined group. Markers reflecting cartilage degradation decreased by −22.4 ± 6.8% in the combined group compared with −10.1 ± 5.9% in the training-only group, producing a between-group mean difference of −12.3 percentage points (95% CI: −14.58 to −10.02; $p < 0.001$), again reflecting a large standardized effect (Cohen's $d = -1.93$) (Table 3). In parallel, biomarkers reflective of cartilage synthesis increased by +18.6 ± 5.2% in the combined group compared with +7.9 ± 4.8% in the training-only group, with a between-group difference of +10.7 percentage points (95% CI: +8.91 to +12.49; $p < 0.001$) and a large effect size (Cohen's $d = +2.14$) (Table 4). Collectively, these findings indicate that while resistance training alone improved symptoms and produced measurable biochemical changes, the addition of collagen peptides was associated with a substantially greater shift toward reduced cartilage degradation and enhanced cartilage synthesis within the 12-week timeframe. No adverse events related to resistance training or supplementation were reported. Adherence to supervised resistance training exceeded 90% in both groups, supporting intervention fidelity and strengthening confidence that observed differences were attributable to the experimental condition rather than differential participation.

Table 1. Baseline Demographic and Clinical Characteristics (n = 120)

Variable	Combined Group (n = 60)	Training Only (n = 60)	Between-Group Test	p-value
Age (years)	58.2 ± 6.4	57.9 ± 6.7	Independent t-test	0.802
Sex (Male/Female), n	28 / 32	30 / 30	Chi-square test	0.713
BMI (kg/m²)	27.6 ± 3.1	27.9 ± 3.4	Independent t-test	0.612
Disease Duration (years)	5.1 ± 2.3	5.3 ± 2.5	Independent t-test	0.661

Table 2. Primary Outcome — Pain Scores at Baseline and 12 Weeks

Time Point	Combined Group (n = 60)	Training Only (n = 60)	Mean Difference (95% CI)	Cohen's d	p-value
Baseline	6.8 ± 1.1	6.7 ± 1.2	+0.10 (−0.32 to +0.52)	0.09	0.637
12 Weeks	3.2 ± 0.9	4.5 ± 1.0	**−1.30 (−1.64 to −0.96)**	**−1.37**	**< 0.001**
Change (12W − Baseline)	−3.6	−2.2	−1.4	—	—

Note: Negative mean difference favors the combined group (lower pain). Change-score SD was not available; therefore, inferential statistics are based on between-group comparisons at each time point.

Table 3. Cartilage Degradation Biomarker — Percentage Change from Baseline to 12 Weeks

Outcome	Combined Group (n = 60)	Training Only (n = 60)	Mean Difference (95% CI)	Cohen's d	p-value
Degradation Biomarker (% Change)	−22.4 ± 6.8	−10.1 ± 5.9	**−12.3 (−14.58 to −10.02)**	**−1.93**	**< 0.001**

Note: Negative values indicate reduction in cartilage degradation marker, favoring the combined group.

Table 4. Cartilage Synthesis Biomarker — Percentage Change from Baseline to 12 Weeks

Outcome	Combined Group (n = 60)	Training Only (n = 60)	Mean Difference (95% CI)	Cohen's d	p-value
Synthesis Biomarker (% Change)	+18.6 ± 5.2	+7.9 ± 4.8	**+10.7 (+8.91 to +12.49)**	**+2.14**	**< 0.001**

Note: Positive values indicate increase in cartilage synthesis marker, favoring the combined group.

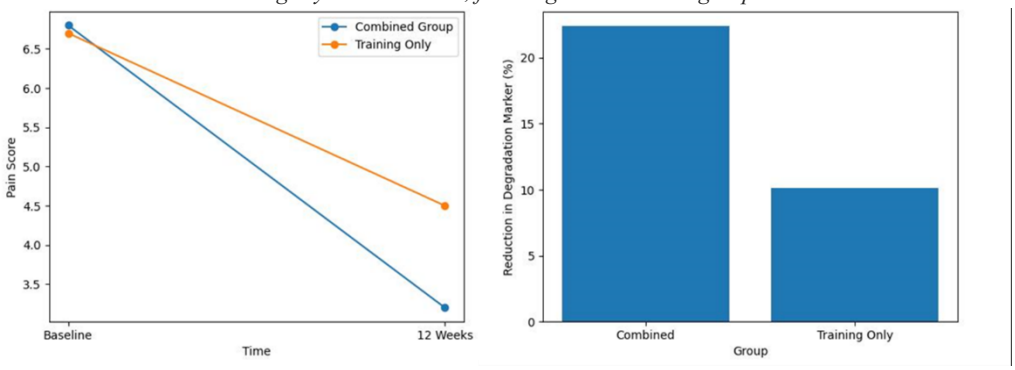

Figure 2 Changes in Pain Scores and Cartilage Degradation Biomarker Following 12 Weeks of Intervention.

Both groups demonstrated improvement over the 12-week period; however, the combined intervention group showed a larger reduction in pain scores and a greater reduction in the cartilage degradation biomarker compared with resistance training alone, indicating superior symptomatic and biochemical response with collagen peptide supplementation.

DISCUSSION

This randomized controlled trial evaluated whether adding daily collagen peptide supplementation to a supervised progressive resistance training program yields incremental benefits in adults with mild to moderate knee osteoarthritis. The findings demonstrated that both groups experienced statistically significant reductions in pain over 12 weeks, consistent with the established role of resistance training as a core conservative intervention for osteoarthritis-related pain. However, participants receiving collagen peptides in addition to resistance training achieved a substantially greater reduction in pain severity at follow-up, with a large between-group effect size, supporting an additive symptomatic benefit beyond exercise alone. These results are aligned with broader evidence that multimodal non-pharmacological strategies can improve osteoarthritis symptom profiles, and they provide clinically relevant support for augmenting exercise therapy with targeted nutritional substrate support in selected populations (9-13).

The additional pain benefit observed with collagen peptide supplementation is biologically plausible. Collagen-derived peptides are absorbed and may contribute amino acids and small peptides implicated in connective tissue remodeling and extracellular matrix homeostasis. In osteoarthritis, progressive cartilage collagen breakdown contributes to structural deterioration and pain generation through altered biomechanics and inflammatory signaling. Nutritional approaches that provide substrate availability during periods of anabolic stimulation—such as exercise—may therefore support tissue-level adaptation, potentially influencing symptom trajectories even over relatively short time horizons. While mechanistic pathways cannot be confirmed from this study design, the magnitude of pain improvement in the combined group suggests that collagen peptide supplementation may meaningfully complement supervised strengthening, particularly in individuals with ongoing symptoms despite exercise exposure (10).

Beyond symptoms, the present trial incorporated serum biomarkers representing cartilage degradation and synthesis as secondary outcomes. Although serum markers cannot replace imaging-based assessment of cartilage structure, they offer a dynamic window into cartilage turnover pathways that may respond earlier than structural endpoints. In this study, both intervention arms demonstrated directional changes consistent with improved cartilage metabolic balance, but the combined collagen plus resistance training group demonstrated significantly larger reductions in degradation markers and larger increases in synthesis markers. This pattern suggests that combined nutritional and mechanical stimuli may promote a shift toward reduced catabolic activity and enhanced anabolic signaling within cartilage-associated pathways, potentially supporting the hypothesis that substrate availability can augment exercise-mediated tissue remodeling (11). Importantly, the biomarker findings were directionally coherent with the clinical response, strengthening confidence that pain improvements were not solely attributable to non-specific effects, although placebo effects cannot be ruled out given the absence of a placebo supplement (12).

The trial findings should also be interpreted in the context of known variability in osteoarthritis biomarkers and clinical outcomes. Biomarker concentrations may be influenced by diurnal variation, physical activity, comorbid metabolic factors, and inflammatory status, and short-term changes do not necessarily translate into sustained cartilage preservation. Accordingly, while the present biomarker results are encouraging, they should be viewed as supportive biological signals rather than definitive evidence of structural disease modification. The interpretation would be strengthened by integrating imaging outcomes such as quantitative MRI cartilage thickness or radiographic progression indices and by extending follow-up duration to determine whether biochemical shifts persist and correlate with longer-term clinical and structural outcomes (13).

Several methodological strengths support the internal validity of this trial. Random allocation produced comparable baseline characteristics across groups, and supervised exercise delivery standardized exposure and likely enhanced adherence and safety. The high completion rate and lack of

reported adverse events suggest feasibility and tolerability of integrating collagen peptide supplementation into supervised resistance training for this population. The inclusion of both clinical and biochemical outcomes allowed a more integrated interpretation than symptom outcomes alone, which is important given that symptomatic improvement does not always correspond to biological changes in cartilage turnover (14). Additionally, this study contributes data from an underrepresented regional setting, improving contextual diversity in osteoarthritis rehabilitation research.

Nevertheless, the study has important limitations that constrain inference and should be addressed in future trials. First, the 12-week duration is adequate to detect symptom change but insufficient to determine long-term durability or structural preservation. Second, the control group did not receive a placebo supplement, and participant blinding was not implemented, which may have inflated pain-related differences through expectation effects. Third, the analysis was performed using an available-case dataset of completers; while attrition was low and unrelated to the intervention, an intention-to-treat strategy and sensitivity analyses would further strengthen robustness. Fourth, the biomarkers were reported as percentage change without parallel reporting of absolute baseline and follow-up biomarker concentrations, limiting cross-study comparability and clinical translation. Finally, functional outcomes such as WOMAC function, KOOS, walking tests, or strength measures were not included, which restricts interpretation of how symptom improvements translate into meaningful activity gains (15-17).

Future research should prioritize longer follow-up, placebo-controlled supplementation arms, and pre-specified analytic models that incorporate baseline adjustment and intention-to-treat handling of missing data. Trials integrating imaging outcomes alongside biomarker panels and clinical metrics would clarify whether short-term metabolic shifts correspond to cartilage preservation or delayed structural progression. Additional work is also needed to refine dosing strategies, timing relative to exercise sessions, and potential subgroup effects, including stratification by BMI, disease severity, metabolic phenotype, and baseline biomarker profile. Such refinements may support personalization of combined exercise and collagen peptide approaches for knee osteoarthritis rehabilitation and facilitate more precise conservative management algorithms (16).

In summary, the present trial suggests that collagen peptide supplementation combined with supervised resistance training provides superior short-term improvements in knee pain and more favorable shifts in cartilage turnover biomarkers compared with resistance training alone. While the findings do not establish structural disease modification, they support a clinically pragmatic, low-risk combined strategy with both symptomatic and biologically supportive signals that warrants confirmation in longer, placebo-controlled, and imaging-integrated trials (17).

CONCLUSION

In adults with mild to moderate knee osteoarthritis, adding daily collagen peptide supplementation to a supervised 12-week resistance training program produced greater improvements in pain and more favorable changes in serum biomarkers reflecting cartilage degradation and synthesis than resistance training alone. These findings support a short-term additive benefit of integrating targeted nutritional substrate support with exercise-based rehabilitation, although confirmation in longer-duration, placebo-controlled studies incorporating functional and imaging outcomes is required to determine durability and structural relevance.

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