Joint Diseases and Related Surgery

Jt Dis Relat Surg
2025;36(1):85-96

ORIGINAL ARTICLE

Effect of supplementation with type 1 and type 3 collagen peptide and type 2 hydrolyzed collagen on osteoarthritis-related pain, quality of life, and physical function: A double-blind, randomized, placebo-controlled study

Ahmet Serhat Genç, MD[1], Ali Kerim Yılmaz, MSc[2], Berna Anıl, MSc[2], Esra Korkmaz Salkılıç, MSc[2], Enes Akdemir, MSc[2], Aykut Sancaklı, MSc[3], Ahmet Mor, MSc[4], Egemen Ermiş, MSc[2], Lale Saka Baraz, MD[5], Nizamettin Güzel, MD[6], Lokman Kehribar, MD[6]

[1]Department of Orthopedics and Traumatology, Samsun Traing and Research Hospital, Samsun, Türkiye
[2]Ondokuz Mayıs University, Faculty of Yaşar Doğu Sport Sciences, Samsun, Türkiye
[3]Department of Leather Engineering, Faculty of Engineering, Ege University, İzmir, Türkiye
[4]Department of Physical Education And Sports, Faculty of Sports Sciences, Sinop University, Sinop, Türkiye
[5]Department of Internal Diseases, Manisa City Hospital, Manisa, Türkiye
[6]Department of Orthopedics and Traumatology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

Osteoarthritis (OA) is characterized by degenerative changes within joint tissues, including morphological alterations and loss of cartilage integrity.[1] Although the onset of the disease is often correlated with age-related joint degeneration, various factors, including obesity, genetic predisposition, and

Received: September 06, 2024
Accepted: October 14, 2024
Published online: November 05, 2024

Correspondence: Egemen Ermiş, MSc. Ondokuz Mayıs Üniversitesi, Yaşar Doğu Spor Bilimleri Fakültesi, 55280 Atakum, Samsun, Türkiye.

E-mail: egemen.ermis@omu.edu.tr

Doi: 10.52312/jdrs.2025.1965

Citation: Genç AS, Yılmaz AK, Anıl B, Korkmaz Salkılıç E, Akdemir E, Sancaklı A, et al. Effect of supplementation with type 1 and type 3 collagen peptide and type 2 hydrolyzed collagen on osteoarthritis-related pain, quality of life, and physical function: A double-blind, randomized, placebo-controlled study. Jt Dis Relat Surg 2025;36(1):85-96. doi: 10.52312/jdrs.2025.1965.

ABSTRACT

Objectives: The aim of this study was to assess the effect of Naturagen® 4 Joint product, containing type 1, 2, and 3 collagen, on pain associated with osteoarthritis (OA) and to evaluate its effects on quality of life and physical functioning.

Patients and methods: This double-blind, randomized, placebo-controlled clinical study included a total of 31 patients (8 males, 23 females; mean age: 53.5±9.1 years; range, 35 to 65 years) with Grade 2-3 OA according to the Kellgren-Lawrence (KL) classification system between June 2023 and November 2023. The patients were divided into two groups: a collagen group (n=16) and a placebo group (n=15). The Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS-PS), Oxford Knee Score (OKS), Tampa Scale for Kinesiophobia (TSK), Short Form Health Survey (SF-12), Foot Function Index (FFI), Timed Up and Go (TUG), 6-Min Walking Test (6MWT), Five Repetition Sit to Stand Test (5STS), Stair Climbing Test (SCT), and Berg Balance Scale (BBS) were used. All tests were performed before and after eight weeks of collagen supplementation.

Results: Eight weeks of collagen supplementation yielded notable enhancements across all osteoarthritis-related pain and quality of life scales evaluated, including VAS, WOMAC, KOOS-PS, OKS, TSK, SF-12, and FFI scores ($p<0.05$). In functional evaluations, there were significant positive effects of collagen use in BBS and 6MWT results ($p<0.05$). In TUG, 5STS, and SCT tests, no significant difference was found between the groups ($p>0.05$).

Conclusion: Our study results suggest that the eight-week collagen-based supplement exerts a favorable effect on pain and quality of life levels, as well as some functional test results.

Keywords: Collagen supplement, osteoarthritis, pain, physical function, quality of life.

stress, can exacerbate OA by inducing low-grade systemic inflammation.[2] During the early stages of the disease, symptoms manifest as irregularities within the collagen matrix and fragmentation of collagen fibers, resulting in higher water content within affected tissues.[3] Furthermore, systematic inflammation and active synovitis play a central role in the pathophysiology of both rheumatoid arthritis and OA, which can be influential in disease progression.[4] This condition manifests with a range of symptoms, including joint stiffness, reduced mobility, and musculoskeletal pain, all of which significantly impact the quality of life for affected individuals.[5-7] Therefore, it is of utmost importance to develop effective treatment and management strategies that consider both the biomechanical and inflammatory components of OA.

Strategies used to treat OA include home physical therapy, physiotherapy, medications, and, in severe cases, joint replacements.[8,9] Common treatment modalities for knee OA include over-the-counter painkillers such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and hyaluronic acid (HA) injections present an alternative option for treating OA by replenishing synovial fluid and restoring joint viscoelasticity.[10] These medications can help relieve pain; however, their effects are usually transient and do not affect the disease process; long-term use may also cause side effects such as stomach disorders, decreased efficacy of diuretics, and inhibition of kidney function.[11,12] Furthermore, numerous studies have indicated that compounds such as glucosamine sulfate, chondroitin sulfate, and collagen derivatives have the potential to alleviate symptoms associated with OA. This evidence supports the notion that these compounds may serve as a viable treatment option for OA.[13,14]

Collagen is a fibrous protein composed of peptides with a unique molecular structure that provides strength and elasticity. It is found in all animals, and its production in the body is thought to decrease with chronological age.[15] It is the most common component of the solid matrix of articular cartilage, and collagen supplementation has been highlighted as an important option to prevent progressive cartilage damage over time and accelerate the healing process after the onset of OA.[16,17] Hydrolyzed collagen peptide and non-hydrolyzed collagen, which are two different forms of collagen supplementation frequently used for the knee joint, have different mechanisms of action.[18] Non-hydrolyzed collagen, a frequently used component in OA treatment, has been shown to benefit by increasing joint comfort in clinical studies.[19] However, as it is not hydrolyzed, absorption is low and, thus, collagen must be hydrolyzed to become a physiologically usable supplement.[20,21] Hydrolyzed collagen contains amino acids and peptides of varying lengths that resist hydrolysis, making them highly bioavailable.[22,23] Numerous studies have demonstrated that the oral intake of hydrolyzed collagen can stimulate chondrocytes and enhance macromolecule synthesis within the extracellular matrix, thereby leading to cartilage regeneration. This process occurs subsequent to collagen absorption from the intestines and its deposition within the articular cartilage.[24] In addition, it has been shown to have beneficial effects on bone, joints, skin, blood sugar, blood pressure, lipid metabolism, and the immune system.[25,26]

The dietary supplement investigated in our study comprises a blend of type 1 and type 3 collagen peptides, along with type 2 hydrolyzed collagen, glucosamine sulfate, chondroitin sulfate, HA, and vitamin C. This formulation stands out for its distinctive composition among collagen supplements. In the present study, we hypothesized that collagen supplementation containing all these components could exert a beneficial impact on symptoms associated with OA. We, therefore, aimed to assess the effects of supplementation with type 1 and type 3 collagen peptides, as well as type 2 hydrolyzed collagen, on OA-related pain, quality of life, and physical functionality.

PATIENTS AND METHODS

Investigational products

The study product was provided by Naturagen® 4 Joint Naturagen İlaç Kozmetik AŞ, Türkiye, registered with the United States (US) Food and Drug Administration (FDA) (Registration No: 12537420128). The product contained 15 stick sachets of 5.75 grams in a box. Naturagen® 4 Joint contained varying amounts of PROFIN® bovine collagen peptides (type 1 and type 3), glucosamine sulfate, chondroitin sulfate, methylsulfonylmethane, malic acid, lemon flavoring, calcium l-ascorbate, HA, maltodextrin, olibanum gumresin extract, chicken hydrolyzed collagen (type 2), silicon dioxide, steviol glycosides, and vitamin C. The ingredient profile of the product is shown in Table I. The placebo product contained 5.2 g of maltodextrin. Both products contained sweeteners with the same flavor. All products had the same appearance, taste, and texture.

TABLE I
Product ingredients and daily doses

Ingredients	Daily intake dose per sachet (mg)
Collagen peptides (type 1, 3)	2000
Glucosamine sulfate	1500
Chondroitin sulfate	750
Methylsulfonylmethane	500
Hyaluronic acid	100
Olibanum gumresin extract	50
Hydrolyzed collagen (type 2)	40
Vitamin C	100

Study design and study population

This double-blind, randomized, placebo-controlled clinical study was conducted at Samsun Traing and Research Hospital, Department of Orthopedics and Traumatology between June 2023 and November 2023. We investigated the effects of eight weeks of use of Naturagen® 4 Joint, a combination of type 1 and type 3 collagen peptide and type 2 hydrolyzed collagen, glucosamine sulfate, chondroitin sulfate, HA, and vitamin C, on various pain and quality of life scales, balance and various functional test results in patients with OA. The study included 31 patients (8 males, 23 females; mean age: 53.5±9.1 years; range, 35 to 65 years) with Grade 2-3 OA according to the Kellgren-Lawrence (KL) classification system. Inclusion and exclusion criteria are listed in Table II and the study flowchart is shown in Figure 1. A written informed consent was obtained from each patient. The study protocol was approved by the Sinop University, Faculty of Medicine, Human Research Ethics Committee (date: 14.09.2023, no: 2023/183). The study was conducted in accordance with the ICH Good Clinical Practice Guidelines and principles of the Declaration of Helsinki. The study was registered at Iran Clinical Trials Registry with the registration number of IRCT20240411061470N1.

At their first visit, in addition to descriptive information and limb lengths, Visual Analog Scale (VAS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Oxford Knee Score (OKS), Tampa Scale for Kinesiophobia (TSK) and Short Form Health Survey (SF-12) scales, Timed Up and Go (TUG) and Stair Climbing Test (SCT) tests were performed. On the day following the first visit, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Foot Function Index (FFI), Berg Balance Scale (BBS) scales, six-minute walk test (6MWT), and Five Repetition Sit to Stand Test (5STS) tests were performed. After completion of the pre-tests, all participants were randomized to one of the two treatment groups using computer-approved software (www.random.org) and divided into collagen (n=16) and placebo (n=15) groups. Blinding of the products was performed using blinding codes in sealed envelopes. The participants and the

TABLE II
Inclusion and exclusion criteria for the study

Inclusion criteria

- Diagnosed with unilateral KL radiographic Grade 2 or 3 knee OA for more than three months
- Non-vegetarian
- Willing to participate in all scheduled visits and tests

Exclusion criteria

KL radiographic Grade 1 or 4 with a diagnosis of knee OA

- Any history of trauma, fracture, or surgery on the index joint
- Evidence or history of clinically significant hematologic, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, or neurologic diseases or malignancies within the last five years
- History of hypersensitivity to the rescue medication or any of the products used in the study
- Active viral or bacterial infection according to clinical examination
- Expected knee arthroscopy or arthroplasty or life-threatening pathology
- Received intra-articular injections or corticosteroids in the target knee joint (the most painful knee at screening) within the last six months
- Patients with intolerance to protein-based foods or supplements, pregnant or breastfeeding women, and those with alcohol dependence

KL: Kellgren-Lawrence; OA: Osteoarthritis.

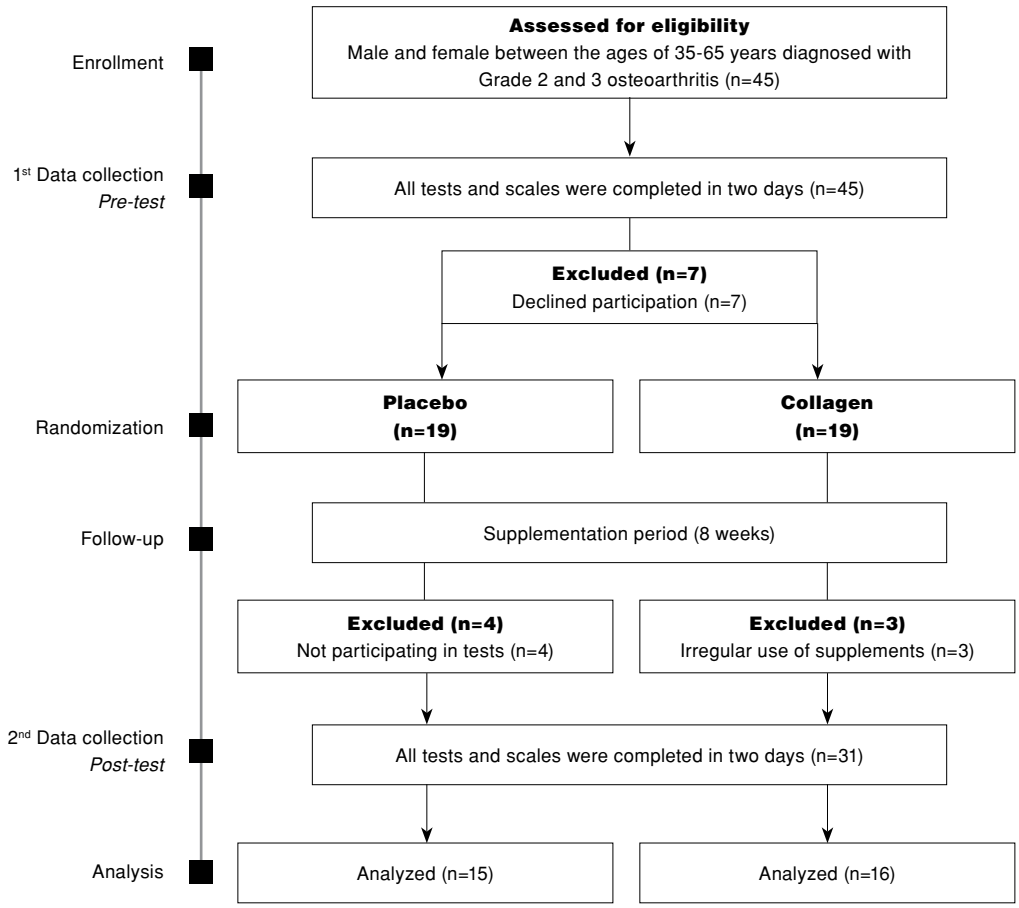

FIGURE 1. Study flowchart.

investigators responsible for data collection were blinded to treatment allocation. The participants were instructed to consume the products according to the manufacturer's recommendation, one sachet per day, dissolved in one glass (200 mL) of water, for a total of eight weeks. For a thorough follow-up process, the participants were assigned diary cards, and their product use was recorded in this way. The participants were also asked to maintain their general daily physical activity levels and not to participate in any physical activity program during the study period. Throughout the study, analgesics were allowed to be used as rescue medication except for 48 h before the measurements. The participants returned after eight weeks of product use, and post-tests were completed on two consecutive days in the same order as the pre-tests. All measurements in the study were performed at the same time of the day (01:00-03:00 PM). The primary endpoint of the study was the successful completion of the final tests after eight weeks of product use, and the secondary endpoints were the patient's unwillingness to continue the study for various reasons, discontinuation of product use earlier than eight weeks, any trauma to the index joint, and the development of hypersensitivity to the product used in the study. In previous studies, collagen supplementation was evaluated at various follow-up periods such as 4, 6, 8, 12, and 24 weeks, and it was predicted that tissue regeneration and treatment effects could be observed at eight weeks of follow-up, although there were changes according to the type of test.[12,13,27–29]

Assessment tools

Pain and quality of life scales

The VAS is a 100-mm line used for self-assessment of knee pain by patients. Patients indicate their pain level by marking a point on the line between 'no pain' and 'excruciating pain.' A higher score indicates greater pain intensity.

The WOMAC is a 24-item scale consisting of three dimensions: pain (five questions), stiffness

(two questions), and physical function (17 questions). It is scored on a five-point Likert scale (none, mild, moderate, severe, extreme). It is calculated by standardizing to a range of values from 0 to 100. A higher score indicates increased pain, stiffness, and functional limitations.

The KOOS-PS scale is used to assess the activities of daily living and physical function of people with OA and knee injuries. All items are scored on a five-point Likert scale from 0-4 (none, mild, moderate, severe, extreme). The maximum score is 100. A score of 0 indicates that there is no problem, and a score of 100 indicates that the knee problem is serious.

The OKS is used to assess pain and functional status and consists of 12 questions about problems the patient has experienced in the knee in the last four weeks. The raw score is a value between 0 and 48. Low scores indicate poor knee function and pain.[30]

The TSK includes 17 questions covering fear of falling and fear of movement and scores range from 1 to 4. Questions 4, 8, 12, and 16 were reversed. A high score (maximum 68) indicates that the patient has a high fear of falling and moving.[31]

The SF-12 consists of two different dimensions: Physical Component Score (PCS) and Mental Component Score (MCS). Both SF-12 PCS and SF-12 MCS are scored between 0 and 100. A higher score indicates better health.

The FFI pain consists of 23 items with three subgroups: pain, disability, and activity limitation. Higher scores indicate more pain, disability, and activity limitation.[32] After summing the scores obtained from the patients' answers, the resulting score is divided by the total maximum score that these questions can receive. The number obtained is multiplied by 100, and the total score is calculated.

Functional tests

The TUG is a simple test which evaluates how quickly one can stand up and sit down. The patient is asked to stand up from a seated position on a standard chair, walk three meters, turn around, and sit back on the chair. The use of assistive devices such as canes is allowed when necessary, and the elapsed time is recorded.

The 6MWT is standardized tool to measure functional capacity. The patients are asked to walk as fast as they can safely in a 30 m corridor for 6 min, with the chance to stop and rest when needed.[33] Patients who regularly use assistive devices such as canes are able to use them during the test. At the end of 6 min, walking distance is recorded in meters.

The 5STS is a simple physical performance test. Before starting the test, the patients are asked to cross their arms across their chest and sit and stand on the chair once. They are, then, asked to sit and stand five times as fast as possible. After five repetitions, the elapsed time is recorded.[34]

TABLE III
Baseline demographic and clinical characteristics of patients

	Placebo (n=15)			Collagen (n=16)		
	n	%	Mean±SD	n	%	Mean±SD
Characteristic						
Age (year)			51.5±11.4			55.4±6
Height (cm)			167±7.3			163.6±7.4
Weight (kg)			87.8±13.1			86.8±15.8
BMI (kg/m^2)			31.6±5			32.4±5
Sex						
Female	11			12		
Male	4			4		
Osteoarthritis side						
Right	5	33		10	63	
Left	10	67		6	37	
Dominant side						
Right	15	100		16	100	
Left	-	-		-	-	

SD: Standard deviation; BMI: Body mass index.

TABLE IV
Intra-group and inter-group analysis of pain, kinesiophobia, and quality of life scores

	Placebo			Collagen			Interaction				
	Pre	Post		Pre	Post		Pre-Pre	Post-Post	Group	Time	Group × time
	Mean±SD	Mean±SD	*p*	Mean±SD	Mean±SD	*p*	*p*	*p*	*p*	*p*	*p*
VAS	7.1±2.1	6.5±2.5	0.289	6.9±2.9	5.5±2.6	0.018*	0.592	0.001*	0.023*	0.302	0.019*
KOOS-PS	15.3±5.5	15.6±5.9	0.882	17.2±6.3	13.3±5.1	<0.028*	0.722	0.003*	0.187	0.811	0.028*
OKS	18.5±8.2	16.8±9.2	0.378	24.5±8	13.3±6.1	<0.001*	0.154	0.001*	0.086	0.005*	<0.001*
Tampa	40.2±10.1	41.7±9.8	0.429	43.1±7.5	38.9±9	0.023*	0.181	0.335	0.956	0.195	<0.001*
SF-12 physical	36±9.9	36.4±8.7	0.894	29.1±11.7	43±11.4	<0.001*	0.179	0.002*	0.414	0.082	<0.001*
SF-12 mental	45.7±9.3	46±8.5	0.909	48.5±8.2	42.2±8.6	0.010*	0.340	0.613	0.751	0.265	0.054
WOMAC pain	6.5±2.9	6.2±3.6	0.791	9.9±3.1	3±1.8	<0.001*	0.057	<0.001*	0.023*	0.012*	<0.001*
WOMAC stiffness	1.9±2.2	2.8±1.9	0.165	3.8±2.4	2.9±1.3	0.148	0.092	0.941	0.401	0.614	0.118
WOMAC physical function	26.3±9.6	24.5±12.2	0.526	35.1±11.4	15.9±6.1	<0.001*	0.197	<0.001*	0.012*	0.002*	<0.001*
WOMAC total	36±12.9	34.9±17.1	0.764	50.8±16.4	21.2±7.7	<0.001*	0.109	<0.001*	0.023*	0.001*	<0.001*

SD: Standard deviation; VAS: Visual Analog Scale; KOOS-PS: Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form; OKS: Oxford knee score; SF-12: Short-Form Health Survey; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index; * p<0.05.

The SCT is a simple functional exercise test. The patients are asked to ascend and descend 10 flights of stairs, as fast as they can without endangering themselves (step height 20 cm). During the test, the patients are allowed to hold on to the bars next to the ladder. The time taken to complete the movement is recorded in sec.

The BBS is a scale developed to assess the risk of falls and loss of balance in patients. A score of 0-4 is given for each item. The total score is 56. A score of 0-20 indicates a high risk of falling, a score of 21-40 indicates a moderate risk of falling, and a score of 41-56 indicates a low risk of falling. A standard chair, a standard step, a 15 m-long corridor, and a stopwatch are used for the test, and the total score is recorded.

Statistical analysis

Study power and sample size calculation were performed using the G*Power version 3.1 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). Accordingly, it would be appropriate to conduct the study with 14 participants in both groups (effect size r: 0.87, lower and upper critical p=0.55, true power=0.91).

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The Shapiro-Wilk test was applied to check the normality of data distribution. Differences in characteristics across groups were assessed using the one-way analysis of variance (ANOVA) test. Group comparisons over time were conducted using a mixed repeated-measures analysis of variance (RM ANOVA), with post-hoc analyses adjusted using the Bonferroni correction. In this study, we considered 'time' (pre- and post-measurements) and 'group' (placebo and collagen) as within-subject and between-subject factors, respectively. We confirmed the sphericity assumption using Mauchly's test; if violated ($p<0.05$), we applied the Greenhouse-Geisser correction. As a key assumption, we also tested the interaction between time and group. A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

Descriptive data of the patients are presented in Table III. There was no statistically significant difference between the placebo and collagen groups ($p>0.05$).

Table IV presents the pre- and post-comparison of pain, kinesiophobia, and quality of life scales in the placebo and collagen groups. Based on these evaluations, the collagen group showed positive results with statistical significance in OCS, SF-12 PCS, WOMAC Pain, WOMAC Physical function and WOMAC Total ($p<0.001$) scores and VAS ($p=0.018$), KOOS-PS ($p=0.028$), TAMPA ($p=0.023$) and SF-12 MCS ($p=0.010$) scores. In the placebo group, no statistically significant difference was observed in any parameter in pre- and post-evaluations, and comparable results were obtained ($p>0.05$).

Figure 2 depicts the evaluation of FFI sub-dimensions of pain, disability, and activity restriction parameters in the placebo and collagen groups on the OA and contralateral sides, both pre- and post-treatment. The collagen group showed significant differences in FFI pain ($p=0.011$), FFI disability ($p=0.009$), and FFI activity restriction ($p=0.003$) scores on the OA side, and positive results were observed in post-evaluations. On the contralateral side of the collagen group, pre- and post-measurements yielded similar results ($p>0.05$). In the placebo group, there was a significant difference in the FFI pain ($p=0.026$) on the OA side and FFI pain ($p=0.023$) on the contralateral side.

Figure 3 shows the pre- and post-comparisons of TUG, 6MWT, 5STS, SCT, and BBS evaluations in placebo and collagen groups. The collagen group showed positive results with significant differences in 6MWT ($p=0.017$) and BBS ($p=0.012$) parameters. In the placebo group, there was no statistically significant difference in any parameter, and pre- and post-evaluations revealed similar results ($p>0.05$).

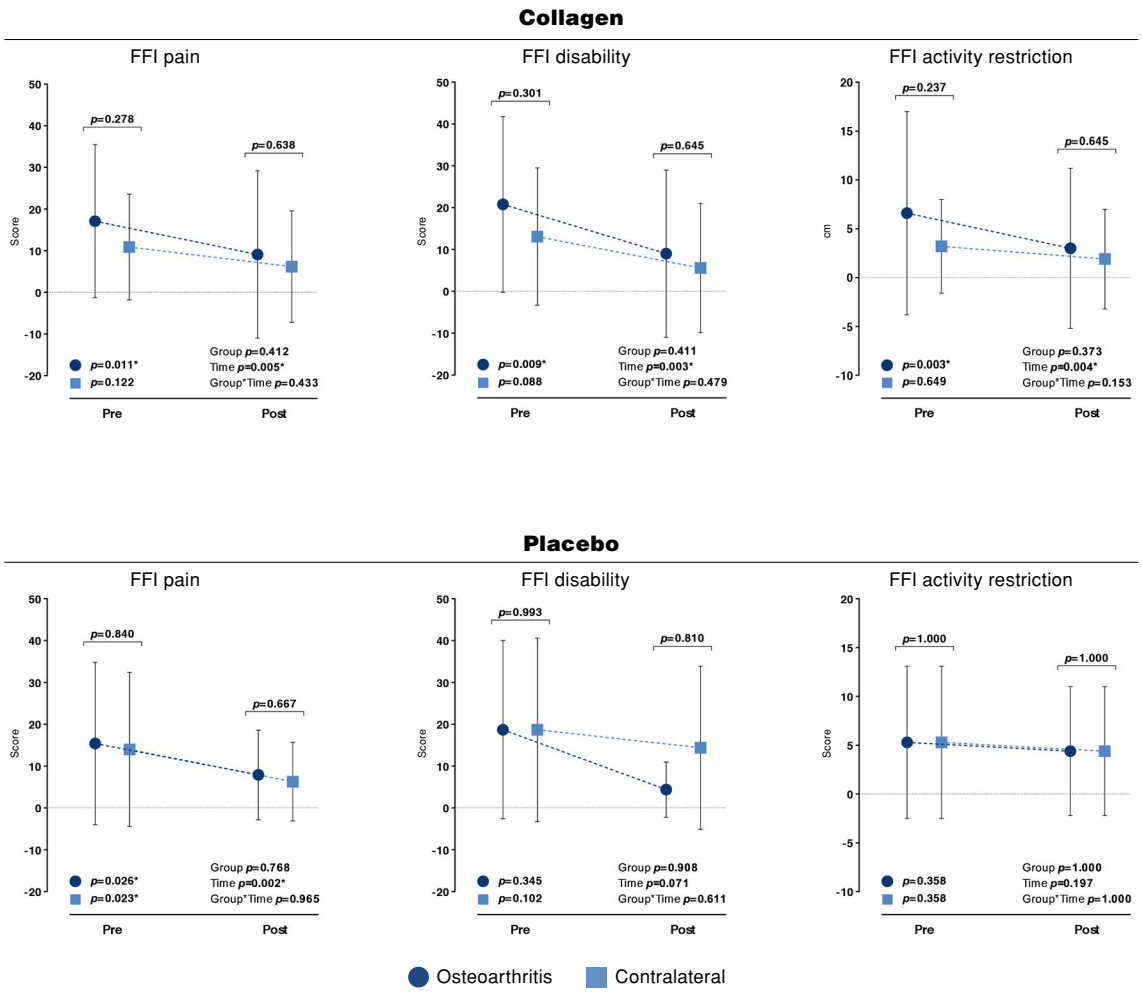

FIGURE 2. Intra-group and inter-group analysis of foot function index results.
FFI: Foot Function Index; * $p<0.05$.

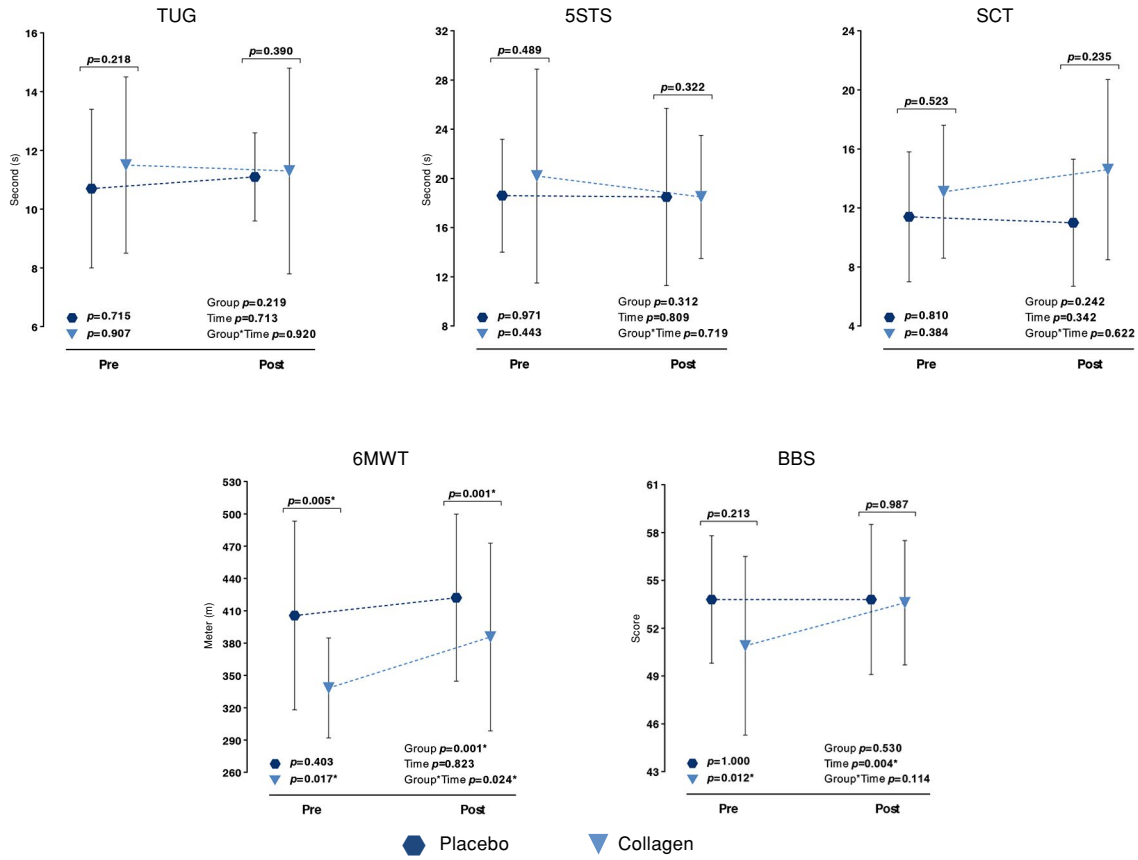

FIGURE 3. Intra-group and inter-group analysis of functional test and scale results.
TUG: Timed Up and Go test; 5STS: Five Repetition Sit to Stand test; SCT: Stair climbing test; 6MWT: Six-minute walk test; BBS: Berg Balance Scale; * p<0.05.

DISCUSSION

In the prenovel supplement formulation containing type 1 and type 3 collagen peptide, type 2 hydrolyzed collagen, glucosamine sulfate, chondroitin sulfate, HA and vitamin C in improving various pain and quality of life metrics, balance, and functional outcomes in patients diagnosed with Grade 2-3 OA according to the KL classification system. The primary finding of the study revealed that eight weeks of supplementation with diverse collagen types elicited statistically significant effects on pain perception, quality of life, and balance scale scores among patients with OA.[35] Nonetheless, the effects of eight weeks of supplementation on functional test results demonstrated variability across different metrics.

Although the exact etiology of OA is unknown, it is associated with inflammation in articular cartilage, which can cause pain and various functional limitations due to abnormal joint structure, and with the myriad adverse effects attributed to the administration of analgesic and anti-inflammatory medications for OA, there has been a notable shift toward investigating safe therapeutic constituents, particularly the potential effects of collagen species, in OA treatment.[36,37]

Many recent studies have investigated the effect of collagen supplementation on OA pain levels, and the results have shown that collagen is an effective method of reducing pain levels.[10,12,13,28,29,37] In our study, both the WOMAC pain and VAS scores indicated that an eight-week collagen supplementation regimen effectively mitigated pain levels associated with OA, consistent with findings from prior research. Beyond pain management, the progression of OA imposes activity limitations that profoundly impact individuals' psychological and social well-being, thereby compromising their overall quality of life. Hence, evaluating the quality of life in OA patients is of paramount importance for gaining deeper insights into the disease trajectory and treatment outcomes.[38] In our study,

many scales such as WOMAC, KOOS-PS, OCS, and SF-12 were used to assess quality of life, and the results in all scales showed that collagen supplementation provided significant increases in quality of life. These results are consistent with previous studies in the literature.[12,39] The positive effects on pain and quality of life can be explained by the protective effect of collagen on cartilage.[12] Collagen has been demonstrated to produce anti-inflammatory cytokines that stimulate chondrocytes and are responsible for the synthesis of cartilage matrix components. This occurs through the induction and migration of regulatory T cells to the site of inflammation and damage.[40] It has also been reported that oral hydrolyzed collagen use increases the appearance of collagen-derived peptides such as Pro-Hyp in human blood, which promotes HA synthesis from synovial cells.[41,42] In addition, hydrolyzed collagen stimulates chondrocytes to produce type 2 collagen and proteoglycan.[43] However, despite all these known physiological effects of collagen supplementation, additional studies are still needed to clarify the basic mechanisms involved in improving OA symptoms.

In addition to collagen, the supplement used in our study also contained HA, glucosamine sulfate, and chondroitin sulfate, which have proven efficacy in the treatment of OA.[14,44] Therefore, besides collagen, it is conceivable that other efficacious components within the product contribute to the observed positive effects of eight weeks of supplementation on pain relief and enhancement of quality of life. However, to gain a more precise understanding of this scenario, it would be necessary to compare the effects of individual components within separate groups. Additionally, researchers have underscored that various factors, including pain and activity limitations, may influence the development of kinesiophobia in individuals.[45,46] In our study, kinesiophobia levels were evaluated using the TSK scale, and significant decreases in kinesiophobia levels were found after collagen supplementation. This result supports the idea that improvements in pain and quality of life levels may also provide positive effects on kinesiophobia levels.

As a reflection of the movement limitation and functional consequences caused by knee OA, loss of balance and consequent fall risk are at the forefront in patients.[47] Indeed, high rates of fall risk have been reported in patients with knee OA in various studies.[48,49] Therefore, the determination of balance levels in OA patients is of utmost importance in terms of revealing the risk status of patients and understanding the level of treatment. In our study, FFI scales, which are thought to reflect possible indirect effects on lower extremity balance performance, and BBS scales were used to understand the direct balance status. Both scale scores showed a significant improvement after collagen supplementation. This showed that therapeutic methods such as collagen supplementation may be effective in preventing risk factors that may lead to serious consequences such as falls in OA patients.

The International Osteoarthritis Research Society (OARSI) recommends the use of various physical performance-based functional assessments for individuals with OA, including tests such as TUG, SCT, and 6MWT.[12,50] Santana et al.[12] evaluated the effects of collagen supplementation on TUG and 6MWT tests in patients with OA and reported that the use of collagen provided significant increases in both test results. In a similar study, Costa et al.[27] concluded that collagen supplementation showed positive effects in both tests. In our study, various tests, such as TUG, SCT, 6MWT, and 5STS, were utilized for functional assessments based on physical performance. Although the results of our study confirmed the significant efficacy of collagen in the 6MWT, similar to the literature, no significant effect was observed in the other tests. Various reasons, such as age differences, sex, and the health status of the knees on the contralateral side, may affect the functional test results. In addition, compared to the scales included in the study, the emergence of effects in functional test results may require longer-term collagen use.

Nonetheless, this study has several limitations, such as the number of subjects in the groups, the age difference of the participants, the lack of sex-specific assessments, the duration of supplement use, and the evaluation of a single product with varying amounts of ingredients. In addition, the fact that various biomarkers associated with OA, such as cartilage oligomeric matrix protein and C-reactive protein, which have an important role in collagen secretion and joint stability, were not included in the study, stands out as another important limitation.

In conclusion, our study results suggest that the supplement containing collagen types and various components that are effective in the treatment of OA exerts favorable effects, particularly on pain, quality of life, and kinesiophobia levels. These results indicate that the use of collagen may provide important

contributions, particularly in terms of pain and quality of life in patients with OA. In addition, it may be promising for clinicians to prefer collagen as a supportive product in the OA treatment process. In future studies, having a higher number of subject groups, keeping the age range in more specific ranges, and including sex-specific evaluations would contribute to a clearer understanding of the effects of collagen supplementation. In addition to the product used in our study, including inter-group comparisons in which the product components are examined separately in addition to the product used in our study may reveal clearer data on how effective the combined use of the components is. In future studies, consideration of various biomarkers associated with collagen and OA, such as cartilage oligomeric matrix protein and C-reactive protein, may provide a clearer physiological rationale for possible improvements in outcomes. In addition to all the supportive conditions listed, extending the supplement intake period and maintaining regular follow-up may contribute to a better understanding of the possible effects of the product in the long term.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Study conception and design, writing: A.S.G., A.K.Y., B.A., E.K.S., E.A., A.S., A.M., E.E., L.S.B., N.G., L.K.; Data collection: A.S.G., L.S.B., N.G., L.K.; Analysis: A.K.Y., A.S., A.M., E.E.; Visualization: B.A., E.K.S., E.A. All authors read and approved the final manuscript.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Liao FX, Yang S, Liu ZH, Bo KD, Xu PF, Chang J. Estrogen receptor is involved in the osteoarthritis mediated by Atg16L1-NLRP3 activation. Jt Dis Relat Surg 2024;35:513-20. doi: 10.52312/jdrs.2024.1247.
2. Mobasheri A, Rayman MP, Gualillo O, Sellam J, van der Kraan P, Fearon U. The role of metabolism in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2017;13:302-11. doi: 10.1038/nrrheum.2017.50.
3. Mobasheri A, Batt M. An update on the pathophysiology of osteoarthritis. Ann Phys Rehabil Med 2016;59:333-9. doi: 10.1016/j.rehab.2016.07.004.
4. Abramoff B, Caldera FE. Osteoarthritis: Pathology, diagnosis, and treatment options. Med Clin North Am 2020;104:293-311. doi: 10.1016/j.mcna.2019.10.007.
5. Kumar H, Pal CP, Sharma YK, Kumar S, Uppal A. Epidemiology of knee osteoarthritis using Kellgren and Lawrence scale in Indian population. J Clin Orthop Trauma 2020;11(Suppl 1):S125-9. doi: 10.1016/j.jcot.2019.05.019.
6. Lespasio MJ, Piuzzi NS, Husni ME, Muschler GF, Guarino A, Mont MA. Knee osteoarthritis: A primer. Perm J 2017;21:16-183. doi: 10.7812/TPP/16-183.
7. Alfieri FM, Silva NCOVE, Battistella LR. Study of the relation between body weight and functional limitations and pain in patients with knee osteoarthritis. Einstein (Sao Paulo) 2017;15:307-12. doi: 10.1590/S1679-45082017AO4082.
8. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/ Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol 2020;72:220-33. doi: 10.1002/art.41142.
9. Bruyère O, Honvo G, Veronese N, Arden NK, Branco J, Curtis EM, et al. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin Arthritis Rheum 2019;49:337-50. doi: 10.1016/j.semarthrit.2019.04.008.
10. Kumar P, Bansal P, Rajnish RK, Sharma S, Dhillon MS, Patel S, et al. Efficacy of undenatured collagen in knee osteoarthritis: Review of the literature with limited meta-analysis. Am J Transl Res 2023;15:5545-55.
11. Yılmaz S, Kurt M, Kekeç AF, Yıldırım A. Effectiveness of gonarthrosis treatment via intra-articular injections of linear vs. cross-linked hyaluronic acids. Jt Dis Relat Surg 2024;35:138-45. doi: 10.52312/jdrs.2023.1403.
12. Santana ÉTN, da Cunha Machado S, Brandão Lima VN, DeSantana Filho VJ, Dos Santos Maciel LY, de Farias Neto JP, et al. Comparison between exercise therapy and non-hydrolyzed collagen (UC-II) in functionality and quality of life in women with knee osteoarthritis: A randomized controlled clinical trial. Wien Klin Wochenschr 2023;135:291-300. doi: 10.1007/s00508-022-02037-8.
13. Luo C, Su W, Song Y, Srivastava S. Efficacy and safety of native type II collagen in modulating knee osteoarthritis symptoms: A randomised, double-blind, placebo-controlled trial. J Exp Orthop 2022;9:123. doi: 10.1186/s40634-022-00559-8.
14. Lomonte ABV, Mendonça JA, de Castro Brandão G, Castro ML. Multicenter, randomized, double-blind clinical trial to evaluate efficacy and safety of combined glucosamine sulfate and chondroitin sulfate capsules for treating knee osteoarthritis. Adv Rheumatol 2018;58:41. doi: 10.1186/s42358-018-0041-9.
15. da Fonseca AG, de Faria Coelho C, Lopes-Martins RAB. Effect of hydrolysed collagen supplementation on knee osteoarthritis: a systematic review. Man Ther Posturology Rehabil J 2022;20:1-9. doi: 10.17784/mtprehabjournal.2022.20.1257.
16. Katz JN. Editorial: Prevalence of arthritis revisited. Arthritis Rheumatol 2018;70:153-4. doi: 10.1002/art.40357.
17. Gao SG, Zeng C, Liu JJ, Tian J, Cheng C, Zhang FJ, et al. Association between Wnt inhibitory factor-1 expression levels in articular cartilage and the disease severity of patients with osteoarthritis of the knee. Exp Ther Med 2016;11:1405-9. doi: 10.3892/etm.2016.3049.
18. Cao C, Xiao Z, Ge C, Wu Y. Animal by-products collagen and derived peptide, as important components of innovative sustainable food systems-a comprehensive review. Crit Rev Food Sci Nutr 2022;62:8703-27. doi: 10.1080/10408398.2021.1931807.

19. Costa AP, Monteiro C, Teixeira VC, da Silva Schwarstzhoupt B, Ferreira PM, Dohnert MB, et al. Correlation between muscle strength and functional improvement after a neuromuscular electrical strengthening associated with undenatured type II collagen in knee osteoarthritis. SN Compr Clin Med 2021;3:1122–32. doi: 10.1007/s42399-021-00830-6.
20. Benito-Ruiz P, Camacho-Zambrano MM, Carrillo-Arcentales JN, Mestanza-Peralta MA, Vallejo-Flores CA, Vargas-López SV, et al. A randomized controlled trial on the efficacy and safety of a food ingredient, collagen hydrolysate, for improving joint comfort. Int J Food Sci Nutr 2009;60 Suppl 2:99-113. doi: 10.1080/09637480802498820.
21. Sibilla S, Godfrey M, Brewer S, Budh-Raja A, Genovese L. An overview of the beneficial effects of hydrolysed collagen as a nutraceutical on skin properties: Scientific background and clinical studies. Open Nutraceuticals J 2015;8:29-42. doi: 10.2174/1876396001508010029.
22. Desai DA, Shendge PN, Anand DSS. Evidence-based nutraceuticals for osteoarthritis: A review. International Journal of Orthopaedics Sciences 2021; 7:846-53. doi: 10.22271/ortho.2021.v7.i2k.2713
23. Larder CE, Iskandar MM, Kubow S. Collagen hydrolysates: A source of bioactive peptides derived from food sources for the treatment of osteoarthritis. Medicines (Basel) 2023;10:50. doi: 10.3390/medicines10090050.
24. Liang CW, Cheng HY, Lee YH, Liao CD, Huang SW. Efficacy and safety of collagen derivatives for osteoarthritis: A trial sequential meta-analysis. Osteoarthritis Cartilage 2024;32:574-84. doi: 10.1016/j.joca.2023.12.010.
25. König D, Oesser S, Scharla S, Zdzieblik D, Gollhofer A. Specific collagen peptides improve bone mineral density and bone markers in postmenopausal women-a randomized controlled study. Nutrients 2018;10:97. doi: 10.3390/nu10010097.
26. Nishikimi A, Koyama YI, Ishihara S, Kobayashi S, Tometsuka C, Kusubata M, et al. Collagen-derived peptides modulate CD4+ T-cell differentiation and suppress allergic responses in mice. Immun Inflamm Dis 2018;6:245-55. doi: 10.1002/iid3.213.
27. Costa AP, Cunha Teixeira V, Pereira M, Mota Ferreira P, Kuplich PA, Dohnert MB, et al. Associated strengthening exercises to undenatured oral type II collagen UCII. a randomized study in patients affected by knee osteoarthritis. Muscle Ligaments Tendons J 2020;10:481. doi: 10.32098/mltj.03.2020.18.
28. Lugo JP, Saiyed ZM, Lane NE. Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: A multicenter randomized, double-blind, placebo-controlled study. Nutr J 2016;15:14. doi: 10.1186/s12937-016-0130-8.
29. Chen CC, Chang SS, Chang CH, Hu CC, Nakao Y, Yong SM, et al. Randomized, double-blind, four-arm pilot study on the effects of chicken essence and type II collagen hydrolysate on joint, bone, and muscle functions. Nutr J 2023;22:17. doi: 10.1186/s12937-023-00837-w.
30. Clement ND, Macdonald D, Burnett R. Predicting patient satisfaction using the Oxford knee score: Where do we draw the line? Arch Orthop Trauma Surg 2013;133:689-94. doi: 10.1007/s00402-013-1728-3.
31. Swinkels-Meewisse EJ, Swinkels RA, Verbeek AL, Vlaeyen JW, Oostendorp RA. Psychometric properties of the Tampa Scale for kinesiophobia and the fear-avoidance beliefs questionnaire in acute low back pain. Man Ther 2003;8:29-36. doi: 10.1054/math.2002.0484.
32. Landorf KB, Keenan AM. An evaluation of two foot-specific, health-related quality-of-life measuring instruments. Foot Ankle Int 2002;23:538-46. doi: 10.1177/107110070202300611.
33. Jakobsen TL, Kehlet H, Bandholm T. Reliability of the 6-min walk test after total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2013;21:2625-8. doi: 10.1007/s00167-012-2054-y.
34. Fisher S, Ottenbacher KJ, Goodwin JS, Graham JE, Ostir GV. Short Physical Performance battery in hospitalized older adults. Aging Clin Exp Res 2009;21:445-52. doi: 10.1007/BF03327444.
35. Atik OŞ. Writing for Joint Diseases and Related Surgery (JDRS): There is something new and interesting in this article! Jt Dis Relat Surg 2023;34:533. doi: 10.52312/jdrs.2023.57916.
36. Lee MH, Kim HM, Chung HC, Kim DU, Lee JH. Low-molecular-weight collagen peptide ameliorates osteoarthritis progression through promoting extracellular matrix synthesis by chondrocytes in a rabbit anterior cruciate ligament transection model. J Microbiol Biotechnol 2021;31:1401-8. doi: 10.4014/jmb.2108.08027.
37. Lin CR, Tsai SHL, Huang KY, Tsai PA, Chou H, Chang SH. Analgesic efficacy of collagen peptide in knee osteoarthritis: A meta-analysis of randomized controlled trials. J Orthop Surg Res 2023;18:694. doi: 10.1186/s13018-023-04182-w.
38. Vitaloni M, Botto-van Bemden A, Sciortino Contreras RM, Scotton D, Bibas M, Quintero M, et al. Global management of patients with knee osteoarthritis begins with quality of life assessment: A systematic review. BMC Musculoskelet Disord 2019;20:493. doi: 10.1186/s12891-019-2895-3.
39. Bongers CCWG, Ten Haaf DSM, Catoire M, Kersten B, Wouters JA, Eijsvogels TMH, et al. Effectiveness of collagen supplementation on pain scores in healthy individuals with self-reported knee pain: A randomized controlled trial. Appl Physiol Nutr Metab 2020;45:793-800. doi: 10.1139/apnm-2019-0654.
40. van Meegeren ME, Roosendaal G, Jansen NW, Wenting MJ, van Wesel AC, van Roon JA, et al. IL-4 alone and in combination with IL-10 protects against blood-induced cartilage damage. Osteoarthritis Cartilage 2012;20:764-72. doi: 10.1016/j.joca.2012.04.002.
41. Sato K, Asai TT, Jimi S. Collagen-derived di-peptide, Prolylhydroxyproline (Pro-Hyp): A new low molecular weight growth-ınitiating factor for specific fibroblasts associated with wound healing. Front Cell Dev Biol 2020;8:548975. doi: 10.3389/fcell.2020.548975.
42. Chae M, Moon CY, Lim SH, Yamashita Y, Yamada H, Ide M, et al. Oral ingestion of AP collagen peptide leads to systemic absorption of Gly-Pro-Hyp, Alleviating H2O2-induced dermal fibroblast aging. J Med Food 2023;26:299-306. doi: 10.1089/jmf.2022.K.0149.
43. Moo EK, Ebrahimi M, Sibole SC, Tanska P, Korhonen RK. The intrinsic quality of proteoglycans, but not collagen fibres, degrades in osteoarthritic cartilage. Acta Biomater 2022;153:178-89. doi: 10.1016/j.actbio.2022.09.002.
44. Nelson FR, Zvirbulis RA, Zonca B, Li KW, Turner SM, Pasierb M, et al. The effects of an oral preparation containing hyaluronic acid (Oralvisc®) on obese knee osteoarthritis

patients determined by pain, function, bradykinin, leptin, inflammatory cytokines, and heavy water analyses. Rheumatol Int 2015;35:43-52. doi: 10.1007/s00296-014-3047-6.
45. Doménech J, Sanchis-Alfonso V, Espejo B. Changes in catastrophizing and kinesiophobia are predictive of changes in disability and pain after treatment in patients with anterior knee pain. Knee Surg Sports Traumatol Arthrosc 2014;22:2295-300. doi: 10.1007/s00167-014-2968-7.
46. Perrot S, Trouvin AP, Rondeau V, Chartier I, Arnaud R, Milon JY, et al. Kinesiophobia and physical therapy-related pain in musculoskeletal pain: A national multicenter cohort study on patients and their general physicians. Joint Bone Spine 2018;85:101-7. doi: 10.1016/j.jbspin.2016.12.014.
47. Hatfield GL, Morrison A, Wenman M, Hammond CA, Hunt MA. Clinical tests of standing balance in the knee osteoarthritis population: Systematic review and meta-analysis. Phys Ther 2016;96:324-37. doi: 10.2522/ptj.20150025.
48. Levinger P, Menz HB, Wee E, Feller JA, Bartlett JR, Bergman NR. Physiological risk factors for falls in people with knee osteoarthritis before and early after knee replacement surgery. Knee Surg Sports Traumatol Arthrosc 2011;19:1082-9. doi: 10.1007/s00167-010-1325-8.
49. Williams SB, Brand CA, Hill KD, Hunt SB, Moran H. Feasibility and outcomes of a home-based exercise program on improving balance and gait stability in women with lower-limb osteoarthritis or rheumatoid arthritis: A pilot study. Arch Phys Med Rehabil 2010;91:106-14. doi: 10.1016/j.apmr.2009.08.150.
50. Dobson F, Hinman RS, Roos EM, Abbott JH, Stratford P, Davis AM, et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis Cartilage 2013;21:1042-52. doi: 10.1016/j.joca.2013.05.002.