UNDENATURED COLLAGEN TYPE II FOR THE 
TREATMENT OF OSTEOARTHRITIS OF THE KNEE

COLÁGENO NÃO HIDROLISADO TIPO II PARA 
TRATAMENTO DA OSTEOARTRITE DO JOELHO

DAVID SADIGURSKY, VICTOR FILARDI STOLZE MAGNAVITA, CLOUD KENNEDY COUTO DE SÁ, HENRIQUE DE SOUSA MONTEIRO, ODDONE FREITAS MELRO BRAGHIROLI, MARCOS ANTÔNIO ALMEIDA MATOS

1. Escola Bahiana de Medicina e Saúde Pública, Salvador, BA, Brazil. 
2. Centro Universitário UniFTC, Salvador, BA, Brazil. 
3. Hospital Geral Ernesto Simões Filho, Salvador, BA, Brazil. 
4. Universidade de São Paulo, São Paulo, SP, Brazil.

ABSTRACT

Objective: To test the hypothesis that undenatured type II collagen (UC-II) relieves pain, quality of life, and joint function in women aged from 60 to 80 years with knee osteoarthritis. Methods: 53 patients in the UC-II treatment group (for 90 days) and 52 in the control group (without UC-II) were evaluated at 1, 30, and 90 days regarding health-related quality of life, pain, and function with questionnaires, anthropometric data, alignment, range of motion, and radiographic analysis. Results: Quality of life increased significantly in the Physical domain in the treatment vs control group. Also, there was a difference between the first and the last evaluation on the pain visual analog scale (−3.8 ± 1.8 versus −1.3 ± 2.0) and on the WOMAC score (−9.5 ± 11.9 versus −1.3 ± 11.1). No variation in the temporal evolution of the Mental domain was found. Conclusion: Pain, joint stiffness, and quality of life (Physical domain) improved with the inclusion of UC-II for 90 days to the therapeutic toolbox for knee osteoarthritis in individuals aged 60 to 80 years. Level of evidence II, Comparative Prospective Study.

Keywords: Osteoarthritis. Collagen Type II. Quality of Life. Pain. Drug Therapy.

INTRODUCTION

Osteoarthritis (OA) is a joint disease common in adults of developed countries, causing musculoskeletal pain and disability resulting in limitation of daily activities, depressed mood, and decrease on health-related quality of life. Among the characteristics of this disease are bone remodeling, formation of osteophytes, wear of the articular cartilage, and varied degrees of synovitis that can affect any joint, especially hips and knees. Currently, clinical guidelines of health services value quality of life as a priority, particularly as part of the management of chronic disease. Thus, the treatment of osteoarthritis prioritize pain relief and functional improvement of affected joints. Therefore, the clinical treatment conducted in either a non-pharmacological or pharmacological manner is prioritized and surgical procedures are only recommended when traditional therapy fails. Some of the non-pharmacological strategies used for the treatment of osteoarthritis to reduce its negative effects on the osteoarticular
system are based on physical exercise, high-protein diet, and weight loss. Such approaches have successfully improved quality of life, emotional well-being, and functional capacity.\(^1\)

The most commonly used drug therapy includes anti-inflammatory drugs, analgesics, weak opioids, and corticosteroids. Although significant for symptom relief, the use of these elements does not predict changes to the evolution of osteoarthritis, and may also present restrictions due to the undesirable side effects.\(^8\) Consequently, drugs currently referred to as disease-modifying antirheumatic drugs (DMARDs) or symptomatic slow-acting drugs for OA (SYSADOAs) – such as glucosamine, chondroitin, diacerein, and more recently type 1 and 2 collagens – have been gaining ground in the pharmaco-logical therapeutic toolbox.\(^9\)

It is believed that oral administration of undenatured type II collagen (UC-II) may improve the chronic inflammatory process by possibly regulating humoral immunity through the oral tolerance mechanism.\(^9\) Small oral doses of antigen favor the suppression of cells mediated by immune responses, while high doses may produce peripheral tolerance. Several animal models have promoted satisfactory effects for autoimmune diseases.\(^10\) These experimental models of arthritis have allowed us to conjecture the occurrence of an induction and migration pathway of Regulatory T cells (Tregs) to inflammatory areas and of cartilaginous damage. In vitro, Tregs produce anti-inflammatory cytokines, stimulating chondrocytes and synthesizing cartilage components.\(^11\)

Although some studies indicate pain relief and improvement in the quality of life with the treatment of osteoarthritis using UC-II,\(^8,11\) evidence on the clinical importance of this drug still requires further clinical studies.\(^12\) Thus, this study aims to test the hypothesis that UC-II relieves pain, improves health-related quality of life, and joint function of individuals aged from 60 to 80 years with OA of the knee.

MATERIALS AND METHODS

This is a prospective and comparative clinical study with randomized block design.

Sample size

Sample size was calculated based on a decrease of 15.4% in the evaluation of the pain visual scale,\(^9\) using a 10% margin of error and adopting 95% as significance level. With these parameters, a sample size of 60 individuals was adopted.

Inclusion and exclusion criteria

A total of 106 patients with knee osteoarthritis were selected and divided equally into two groups (with UC-II and control group without UC-II).

All participants were aged from 60 to 80 years, with clinical suspicion and radiological diagnosis of knee osteoarthritis, who accepted conservative/traditional treatment for the study period, and who agreed not to start another treatment. Patient were excluded from the study if they had history of allergic reaction to any of the prescribed drugs, patients diagnosed with secondary inflammatory arthritis, previous knee infection, marked angular deformities, or if they discontinued the treatment stipulated for the study.

Procedures

Patients were randomly distributed into two groups. The experimental group used UC-II (40 mg daily) for 90 days, whereas the comparative group did not use the supplement. Both groups were submitted to standard physical therapy treatment (kinesiotherapy with closed chain exercises, twice a week) and received simple analgesic and weak opioid for pain relief, when necessary; participants also were followed by the institution’s nutritionist for nutritional guidance and weight control.

Evaluations were performed on day 1 and after the intervention (30 and 90 days). In the initial evaluation, demographic and social data of the patient were collected, along with the level of physical activity, nutritional history, and use of medication and dietary supplements. During physical evaluation, data were collected on range of motion (degrees), alignment of the lower limb (degrees), joint effusion, and measurement of the thigh (cm), and abdominal perimeter (cm). Health-related quality of life assessments were performed with the SF-12 questionnaire (12-item Health Survey);\(^13\) pain levels, with the Visual Analog Scale (VAS); and function, with the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) questionnaire.\(^14\) Finally, all patients underwent radiographic evaluation (front, profile, monopodalic, and axial patellar support) for analysis of knee osteoarthritis degree, the Kellgren-Lawrence classification was used.\(^15\)

In the final evaluation, in addition to the procedures common to the other moments of the evaluation, data were also recorded on the presence of UC-II side effects, the regular or non-use of the medication, and the effective follow-up of the recommended physical therapy treatment.

Instruments used

The SF-12—developed by Ware, Kosinski, and Keller in 1994—\(^16\) is used to evaluate the different domains that determine health-related quality of life, considering the individual’s perception of aspects of their physical and mental health in the last four weeks. The authors consider this questionnaire as more appropriate for evaluating individuals that are affected by diseases involving the musculoskeletal system.\(^13\)

The WOMAC questionnaire was used to identify and to classify pain and joint stiffness and function.\(^14\) The Visual Analog Scale (VAS) was used to measure pain.\(^17\)

Statistics

The primary analysis was performed according to treatment intention and, therefore, included all patients. The baseline characteristics of the groups were reported using frequency and percentage for categorical variables and measures of central tendency and dispersion for continuous variables. Data normality was evaluated by graphical analysis and the Shapiro-Wilk test.

A mixed 2-way analysis of variance (ANOVA) evaluated the combined effect of time and intervention. The sample presented few outliers (maximum of four for mental domain of the SF-12 score), which were reviewed to confirm the values. After the end of the analyses, standardized residues were evaluated, confirming the outliers, which were then excluded to avoid influence on the results. When normality of residues was obtained, no relevant difference in the results was identified. Thus, after a joint critical analysis by the researchers and statistical consultants, it was chosen to maintain the results of the complete sample. Levene’s test (p < 0.05) confirmed the homogeneity of variances, but WOMAC, VAS, and mental domain scores of the SF-12 did not present covariance homogeneity, which was evaluated by the Box’s M test. Researchers chose to proceed with the analysis. In cases in which the Mauchly test indicated that the premise of scouting was not reached (WOMAC, EVA, and Mental domain of the SF-12), the Greenhouse-Geisser correction was adopted. All analyses were performed in the software Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) 21.0 version.
Ethical aspects

The participants were informed about the procedures performed and objectives of the study, being free to abandon the research at any time.

As benefits of participating in this research, adequate treatment and follow-up of patients with osteoarthritis of the knee were provided, while presenting the options available in the treatment of the disease. The study followed the standards of ethical conduct for research contained in National Commission for Research Ethics – CONEP Resolution 466/12, and the project was approved by the FTC/IMES Research Ethics Committee.

All medications and treatments instituted were provided to the patient, as part of the list of medications used as a routine for all patients with osteoarthritis of the knee. The UC-II provided at a dose of 40 mg daily for a period of 90 days is considered as a nutraceutical, and is authorized for commercialization by the Brazilian Health Regulatory Agency – ANVISA, being part of the therapeutic toolbox demonstrated in the literature.

RESULTS

Data from one member of the control group were excluded for non-attendance in the last evaluation. Thus, 53 patients from the UC-II treatment group and 52 of the control group completed the study. As shown in Table 1, the groups were equivalent at the first moment.

There was no significant interaction between time and intervention in the mental domain of the SF-12 score, F (1.103, 154,232) = 0.007, p = 0.978, partial η2 < 0.001, ε = 0.749. The analysis of the main effects of time did not indicate statistically significant difference during the temporal evaluation, F (1.103, 154,232) = 0.147, p = 0.801, partial η2 < 0.001. The analysis of the intervention showed a statistically significant difference between the groups, F (1.103) = 9.424, p = 0.003, partial η2 < 0.084.

In the other scores (WOMAC, VAS, and Physical domain of the SF-12) a statistically significant interaction between time and intervention was identified. Table 2 shows the results of simple main effects analyses.

DISCUSSION

The main results of our study indicate that pain, joint stiffness, and quality of life (Physical domain) improved with the inclusion of UC-II —to the therapeutic toolbox—for 90 days for knee osteoarthritis in individuals aged 60 to 80 years. However, the evaluation of the quality of life revealed that only the physical health component was significantly altered, and no difference was found in the intergroup mental health domain.

Osteoarthritis is the most prevalent form of arthritis in individuals older than 60 years, with great repercussion on pain, functional capacity, and quality of life. The current absence of a cure for this condition justifies the investment in resources to control and/or to mitigate its negative effects on individuals.

Although further studies are necessary to determine the mechanism of UC-II on osteoarthritis cases, it is believed that UC-II activates immune cells in the Peyer's patch, with consequent induction of UC-II on osteoarthritis cases, it is believed that UC-II activates T cells in regulatory T cells (Treg) for type II collagen. When Treg cells migrate, they recognize type II collagen in the articular cartilage and secrete anti-inflammatory mediators and inducers of cartilage matrix repair. Moreover, when compared to the other types of collagen, UC-II has active epitopes—smaller part of antigen with the potential to generate the immune response.

---

**Table 1. Baseline characteristics.**

|   | Total (n = 105) | Control (n = 52) | UC2 (n = 53) | P-value |
|---|----------------|-----------------|-------------|--------|
| Sex | Female | 69 (65.7) | 34 (65.4) | 35 (66.0) | 0.944 |
|     | Male   | 36 (34.3) | 18 (34.6) | 18 (34.0) |       |
| Age | Mean ± Standard Deviation | 68.6 ± 5.6 | 68.6 ± 6.0 | 68.7 ± 5.3 | 0.954 |

**Table 2. Scores of function, pain, and quality of life in follow-ups of 1 and 3 months, with intergroup and temporal comparison.**

| Outcomes | Baseline | 30 days | 90 days | P-value | Difference 90 days - baseline |
|----------|----------|---------|---------|--------|-----------------------------|
| VAS      | Control  | 7.3 ± 0.7 | 6.2 ± 1.2 | 6.0 ± 1.8 | <0.001 | -1.3 ± 2.0 |
|          | UC-II    | 7.1 ± 0.9 | 5.1 ± 1.3 | 3.4 ± 1.6 | <0.001 | -3.8 ± 1.8 |
|          | p-value 1| 0.268    | <0.001   | <0.001   |       | <0.001        |
| SF-12 Physical | Control | 31.5 ± 6.3 | 34.2 ± 7.8 | 33.0 ± 6.2 | 0.046 | 1.5 ± 7.2 |
|          | UC-II    | 29.5 ± 7.1 | 36.5 ± 9.6 | 45.6 ± 8.0 | <0.001 | 16.0 ± 7.9 |
|          | p-value 1| 0.145    | 0.180    | <0.001   |       | <0.001        |
| SF-12 Mental | Control | 50.3 ± 10.0 | 50.7 ± 9.8 | 50.1 ± 11.0 | 0.801 | -0.2 ± 7.4 |
|          | UC-II    | 44.8 ± 11.2 | 45.1 ± 10.3 | 44.8 ± 10.8 | <0.003 | 0.0 ± 13.4 |
|          | p-value 1| -        | -        | -        |       | 0.924          |
| WOMAC   | Control  | 58.6 ± 14.3 | 56.7 ± 15.5 | 57.3 ± 16.5 | 0.370 | -1.3 ± 11.1 |
|          | UC-II    | 54.0 ± 16.6 | 50.8 ± 14.6 | 44.6 ± 12.0 | <0.001 | -9.5 ± 11.9 |
|          | p-value 1| 0.140    | 0.034    | <0.001   |       | <0.001        |
| WOMAC - Pain | Control | 11.9 ± 3.6 | 10.9 ± 4.0 | 11.0 ± 4.7 | -     | -1.0 ± 3.8 |
|          | UC-II    | 12.0 ± 4.2 | 9.5 ± 4.0 | 5.4 ± 3.5 | -     | -6.6 ± 4.8 |
|          | p-value 1| 0.901    | 0.073    | <0.001   | <0.001 |       |
| WOMAC - Stiffness | Control | 3.6 ± 1.2 | 3.6 ± 1.3 | 3.7 ± 1.3 | -     | 0.1 ± 1.1 |
|          | UC-II    | 3.7 ± 1.4 | 3.5 ± 1.6 | 3.2 ± 1.3 | -     | -0.5 ± 0.9 |
|          | p-value 1| 0.685    | 0.661    | 0.034    |       | 0.001        |
| WOMAC - Function | Control | 40.7 ± 10.4 | 39.7 ± 9.6 | 40.3 ± 11.2 | -     | -0.4 ± 7.6 |
|          | UC-II    | 37.3 ± 11.6 | 35.2 ± 11.5 | 34.2 ± 9.8 | -     | -3.0 ± 6.2 |
|          | p-value 1| 0.114    | 0.029    | 0.004    |       | 0.056        |

P-value 1: comparison between groups at different times or temporal difference; p-value 2: temporal comparison —ANOVA of repeated measures for each group separately (simple main effects) when non-significant interaction in 2-way ANOVA with repeated measures or for main effects; Time: **Group.
Crowley et al.8 evaluated the safety and efficacy of UC-II in the treatment of knee osteoarthritis compared to a combination of other nutraceuticals. For this purpose, they performed the 90-day protocol and found that UC-II was better than the combination of glycosamine and condroitin on physical capacity (indicated, for example, by the improvement in walking on a flat surface and in performing heavy household tasks), functionality, and several aspects of pain. Notably, unlike our study, Crowley et al.,8 included young adults and their sample could not represent the population with a greater intensity of pain. Moreover, Bakilan et al.20 not only evaluated the effect of UC-II associated with acetaminophen on symptomatology in knee osteoarthritis, but also pioneered its effect on biochemical markers of cartilage degradation. In this study, the follow-up period was also 90 days and patients aged 45 to 70 years were included. Despite finding improvement in indicators of pain, function, and health-related quality of life, no improvement in biochemical markers of cartilage degradation was identified. The authors highlight the sample size and the short follow-up time as main limitations of the study.

In an experimental study with longer follow-up period (180 days) and analyses of cartilage regeneration markers, Lugo et al.11 evaluated the efficacy and tolerability of UC-II in osteoarthritis. Significant improvement in pain, stiffness, and functionality was observed, but no intra- and intergroup distinction was found for cartilage regeneration and inflammatory markers and synovial fluid biomarkers. Although pain, functioning, and quality of life are variables that are related to each other, in our study the use of UC-II showed a significant change in pain perception, but no statistically significant differences were detected between the groups in the Mental domain of the SF-12 quality of life score and functioning by WOMAC in the evaluated period. Also, in previous studies,8,11 no relationship was found for the modification of functioning, quality of life, and pain scores with markers of morphofunctional cartilage health. The greatest limitation of our study was the non-inclusion of placebo element in the control group. Although the subjects were randomized into the groups and their equivalence was demonstrated by comparing several variables before the beginning of the protocols, it is known that placebo can play an important role and, consequently, become a confounding factor. In a previous study with nutraceuticals, a high response rate to placebo was found.21 Another important factor concerns information bias. Firstly, the evaluators were not blind. Secondly, although validated instruments have been used and have been employed by previously trained evaluators, the use of questionnaires presents potential information bias due to possible distortions in the interpretation of questions and answers, besides presenting possible cultural bias in the measurements, justified by differences in national and cultural contexts.22

Finally, we emphasize the need for further studies with longer periods using the UC-II, with inclusion of objective measures, with a sample of sufficient size to stratify groups regarding the severity of pain and involvement of knee osteoarthritis. We also suggest the inclusion of long-term UC-II tolerability assessment.

**CONCLUSION**

The main results of our study indicate that pain, joint stiffness, and quality of life (Physical domain) improved with the inclusion of UC-II to the therapeutic toolbox for 90 days for knee osteoarthritis in individuals aged 60 to 80 years.

---

**AUTHORS’ CONTRIBUTIONS:** Each author contributed individually and significantly to the development of this article. DS: intellectual concept of the article, preparation of the research project, writing of the article, review, and patients’ follow-up; VFSM: data collection, data analysis, and writing of articles; CKCS, HSM, and OFMB: statistical analysis and review of the article; MAAM: review of the article and of any intellectual concept of the article.

**REFERENCES**

1. Dagenais S, Garbedian S, Wai EK. Systematic review of the prevalence of radiographic primary hip osteoarthritis. Clin Orthop Relat Res. 2009;467(3):623-37.
2. Chevalier X, Eymard F, Richette P. Biologic agents in osteoarthritis: hopes and disappointments. Nat Rev Rheumatol. 2013;9(7):400-10.
3. Zhang W, Doherty M, Peat G, Bierma-Zeinstra MA, Arden NK, Bresnihan B, et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Ann Rheum Dis. 2010;69(3):483-9.
4. Abramson SB, Attur M, Yazici Y. Prospects for disease modification in osteoarthritis. Nat Clin Pract Rheumatol. 2006;2(6):304-12.

---

**Table 3. Differences in the scores of function, pain, and quality of life of baseline measurements, 1 and 3 months with comparison between groups and 95% CI.**

|                  | (3 months - baseline) | (1 month - baseline) | (3 months - 1 month) |
|------------------|-----------------------|----------------------|----------------------|
| **VAS**          | -2.4 (-3.2 - -1.7)    | -0.9 (-1.5 - -0.4)   | -1.5 (-2.3 - -0.7)   |
|                  | < 0.001               | 0.002                | 0.001                |
| **Control**      | -1.3 2.0              | -1.1 1.4             | -0.2 2.3             |
| **UC-II**        | -3.8 1.8              | -2.0 1.5             | -1.7 1.7             |
| **SF-12 Physical** | 14.5 (11.6 - 17.5)    | 4.2 (1.6 - 6.9)      | 10.3 (7.13.5)        |
|                  | < 0.001               | 0.002                | < 0.001              |
| **Control**      | 1.5 7.2               | 2.7 6.2              | -1.2 8.9             |
| **UC-II**        | 16.0 7.9              | 6.9 7.5              | 9.1 7.8              |
| **SF-12 Mental** | 0.2 (-4 - 4.4)        | 0 (-2.3 - 2.4)       | 0.2 (-3.6 - 4)       |
|                  | 0.924                 | 0.981                | 0.928                |
| **Control**      | -0.2 7.4              | 0.3 4.6              | -0.6 5.8             |
| **UC-II**        | 0.0 13.4              | 0.4 7.2              | -0.4 12.6            |
| **WOMAC Pain**   | -8.2 (-12.6 - -3.7)   | -1.4 (-4.7 - 1.9)    | -6.8 (-10.5 - -3.1)  |
|                  | < 0.001               | 0.411                | < 0.001              |
| **Control**      | -1.3 11.1             | -1.9 6.7             | 0.6 11.4             |
| **UC-II**        | -9.5 11.9             | -3.3 10.2            | -6.2 7.3             |
| **WOMAC Stiffness** | -5.7 (-7.3 - -4)     | -1.5 (-2.8 - -0.2)   | -4.2 (-5.4 - -2.9)   |
|                  | < 0.001               | 0.024                | < 0.001              |
| **Control**      | -1.0 3.8              | -1.0 2.9             | 0.0 3.3              |
| **UC-II**        | -6.8 4.8              | -2.5 3.8             | -4.1 3.4             |
| **WOMAC Function** | -0.6 (-1.0 - -0.3)   | -0.2 (-0.6 - 0.1)    | -0.4 (-0.8 - 0)      |
|                  | 0.001                 | 0.195                | 0.033                |
| **Control**      | 0.1 1.1               | 0.0 0.8              | 0.1 0.9              |
| **UC-II**        | -0.5 0.9              | -0.2 1.0             | -0.3 1.1             |
| **WOMAC**        | -2.6 (-5.3 - 0.1)     | -1.1 (-3.7 - 1.4)    | -1.5 (-4.1)          |
|                  | 0.056                 | 0.381                | 0.244                |
| **Control**      | -0.4 7.6              | -1.0 4.9             | 0.6 7.2              |
| **UC-II**        | -3.0 6.2              | -2.1 7.8             | -0.9 5.9             |

All data is showed as ± standard deviation unless specified.
9. Van Baarsen LGM, Lebre MC, Van der Coelen D, Aarrass S, Tang MW, Ramwadhdoebe TH, et al. Heterogeneous expression pattern of interleukin 17A (IL-17A), IL-17F and their receptors in synovium of rheumatoid arthritis, psoriatic arthritis and osteoarthritis: possible explanation for nonresponse to anti-IL-17 therapy? Arthritis Res Ther. 2014;16(4):426.

10. Nagler-Anderson C, Bober LA, Robinson ME, Siskind GW, Thorbecke GJ. Suppression of type II collagen-induced arthritis by intragastric administration of soluble Type II Collagen. Proc Natl Acad Sci U S A. 1986;83(19):7443-6.

11. 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.

12. Van Vijven JPJ, Luijsterburg PAJ, Verhagen AP, Van Osch GJVM, Kloppenburg M, Bierma-Zeinstra SMA. Symptomatic and chondroprotective treatment with collagen derivatives in osteoarthritis: a systematic review. Osteoarthritis Cartilage. 2012;20(8):809-21.

13. Silveira MF, Almeida JC, Freire RS, Haikal DS, Martins AEBL. Propriedades psicométricas do instrumento de avaliação da qualidade de vida: 12-item health survey (SF-12). Cien Saude Colet. 2013;18(7):1923-31.

14. Yang KGA, Rajmakers NJH, Verbout AJ, Dherm WJA, Saris DBF. Validation of the short-form WOMAC function scale for the evaluation of osteoarthritis of the knee. J Bone Joint Surg Br. 2007;89-B(1):50-6.

15. Keiligren JH, Lawrence JS. Radiological assessment of osteo-arthritis. Ann Rheum Dis. 1957;16(4):494-502.

16. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34(3):220-33.

17. Bodian CA, Freedman G, Hossain S, Eisenkraft JB, Beilin Y. The visual analog scale for pain: clinical significance in postoperative patients. Anesthesiology. 2001;95(6):1356-61.

18. Gencoglu H, Orhan C, Sahin E, Sahin K. Undenatured Type II Collagen (UC-II) in joint health and disease: a review on the current knowledge of companion animals. Animals (Basel). 2020;10(4):697.

19. Bagchi D, Misner B, Bagchi M, Kothari SC, Downs BW, Fafard RD, Preuss HG. Effects of orally administered undenatured type II collagen against arthritic inflammatory diseases: a mechanistic exploration. Int J Clin Pharmacol Res. 2002;22(3-4):101-10.

20. Baklan F, Armagan O, Ozgen M, Tascioglu F, Boluk O, Alatas O. Effects of native type II collagen treatment on knee osteoarthritis: a randomized controlled trial. Eurasian J Med. 2016;48(2):95-101.

21. Ciegge DO, Reda DJ, Harris CL, Klein MA, O’Dell JR, Hooper MM, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006;354(8):796-806.

22. Bullinger M, Anderson R, Cella D, Aaronson N. Developing and evaluating cross-cultural instruments from minimum requirements to optimal models. Qual Life Res. 1993;2(6):451-9.