Original Article The Eurasian Journal of Medicine Eurasian J Med 2016; 48: 95-101

Effects of Native Type II Collagen Treatment on Knee Osteoarthritis: A Randomized Controlled Trial

Diz Osteoartritli Hastalarda Nativ Tip 2 Kollajen Tedavisinin Değerlendirilmesi: Randomize Kontrollü Çalışma

Fulya Bakilan[1], Onur Armagan[2], Merih Ozgen[2], Funda Tascioglu[2], Ozge Bolluk[3], Ozkan Alatas[4]

[1]Department of Physical Medicine and Rehabilitation of Yerkoy/Yozgat Public Hospital, Yozgat, Turkey
[2]Department of Physical Medicine and Rehabilitation, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey
[3]Department of Biostatistics, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey
[4]Department of Biochemistry, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey

Abstract

Objective: The aim of this randomized controlled study was to evaluate the efficacy of oral native type II collagen treatment on the symptoms and biological markers of cartilage degradation, when given concomitantly with acetaminophen in patients with knee osteoarthritis.

Materials and Methods: Thirty-nine patients diagnosed with knee osteoarthritis were included and randomly distributed into two groups: one treated with 1500 mg/day of acetaminophen (group AC; n=19) and the other treated with 1500 mg/day of acetaminophen plus 10 mg/day of native type II collagen (group AC+CII; n=20) for 3 months. Visual Analogue Scale (VAS) at rest and during walking, Western Ontario McMaster (WOMAC) pain, WOMAC function, and Short Form-36 (SF-36) scores, were recorded. Coll2-1, Coll2-1NO2 and Fibulin-3 levels were quantified in urine as biomarkers of disease progression. ClinicalTrials.gov: NCT02237989.

Results: After 3 months of treatment, significant improvements compared to baseline were reported in joint pain (VAS walking), function (WOMAC) and quality of life (SF-36) in the AC+CII group, while only improvements in some subscales of the SF-36 survey and VAS walking were detected in the AC group. Comparisons between the groups revealed a significant difference in VAS walking score in favour of the AC+CII group as compared to AC group. Biochemical markers of cartilage degradation in urine did not significantly improve in any of the groups.

Conclusion: All in all, these results suggest that native type II collagen treatment combined with acetaminophen is superior to only acetaminophen for symptomatic treatment of patients with knee osteoarthritis.

Keywords: Acetaminophen, knee osteoarthritis, native type II collagen

Öz

Amaç: Bu çalışmanın amacı, diz osteoartriti olan hastalarda, asetaminofen ile eş zamanlı olarak verilen oral native tip 2 kollajen tedavisinin, semptomlar ve kartilaj yıkımını gösteren biyolojik markerlar üzerine etkisini değerlendirmektir.

Gereç ve Yöntem: Otuz dokuz diz osteoartritli hasta çalışmaya alındı ve randomize olarak 2 gruba ayrıldı: bir gruba 3 ay boyunca 1500 mg/gün asetaminofen verilirken (grup AS; n=19), diğer gruba ise 3 ay boyunca 1500 mg/gün asetaminofene ek olarak 10 mg/gün nativ tip 2 kollajen verildi (grup AS+KII; n=20). Tedavi öncesinde ve sonrasında hastalar, istirahat ve yürüyüş Vizüel Analog Skalaları (VAS), Western Ontario McMaster (WOMAC), Kısa Form-36 (SF-36) ve kartilaj yıkımını gösteren idrardaki Coll2-1, Coll2-1NO2 and Fibulin-3 düzeyleri ile değerlendirildi. ClinicalTrials.gov: NCT02237989.

Bulgular: Üç aylık tedavi sonrasında, tedavi öncesine gore grup AS+KII' de eklem ağrısı (VAS yürüme), WOMAC fonksiyonda ve yaşam kalitesinde (SF-36) istatistiksel olarak anlamlı iyileşme gözlenirken, grup AS' de ise eklem ağrısı (VAS yürüme) ve yaşam kalitesinde (SF-36) iyileşme gözlendi. Gruplararası karşılaştırmada ise; VAS yürüme skorlarında AS+KII lehine istatistiksel açıdan anlamlı bir iyileşme saptandı. Kartilaj yıkımını gösteren biyokimyasal markerlar açısında grup içi ve gruplararası karşılaştırmada bir fark saptanmadı.

Sonuç: Çalışma sonuçları, diz osteoartritli hastalarda, asetaminofen tedavisine eklenen native tip 2 kollajen tedavisinin, semptomları baskılamada, yalnızca asetaminofen alan hastalara göre daha etkili olduğunu göstermiştir.

Anahtar Kelimeler: Asetaminofen, diz osteoartriti, nativ tip 2 kollajen

This study was presented at the 3rd Medical Rehabilitation Congress, Ankara, Turkey, 15-18 November 2012.

Received: February 16, 2015 / **Accepted:** June 04, 2015

Correspondence to: Fulya Bakılan E-mail: fulyabakilan@gmail.com

DOI:10.5152/eurasianjmed.2015.15030

Introduction

Osteoarthritis (OA) is one of the most common joint diseases and is a significant cause of disability [1]. Degenerative changes are observed in both articular cartilage and subchondral bone. In cartilage, the imbalance between synthesis and degradation leads to cartilage destruction [2]. Many researches focus on the underlying mechanisms of cartilage destruction and thereby numerous pharmaceutical and nutraceutical agents have been developed with the aim to delay the progression of structural changes in OA cartilage [3].

The main structural component of the cartilage tissue is collagen type 2. Degradation products of this protein in urine correlate with the progression of articular damage in osteoarthritis [4]. Native type II collagen is a nutraceutical ingredient derived from chicken sternum cartilage. Orally taken native type II collagen antigens interact with Peyer's patches in the gut associated lymphoid tissue, resulting in turning off the T-cell attack to the structural protein collagen type 2 in the cartilage. This desensitization process in Peyer's patch, also known as oral tolerance, avoids the recognition of endogenous collagen type 2 in the cartilage as antigen by the immune system [5, 6]. Considering this mechanism of action, native type II collagen may have positive effects on inflammation and degradation in joint diseases.

Previous studies have shown that native type II collagen has positive effects in the treatment of early rheumatoid arthritis [7-9]. A few studies have evaluated the efficacy of native type II collagen in osteoarthritis. In animal trials, it has been found effective in reducing arthritic pain [10-12]. In human trials, native type II collagen has been found effective in increasing functional status and reducing pain [13, 14]. In addition to symptomatic effects, the study of Scarpellini et al. [14] showed a reduction of the urinary levels of C-terminal telopeptide of type 2 collagen (CTX-2) which is related with the cartilage degeneration in osteoarthritis.

Considering its symptomatic and structural effect on the cartilage, native type II collagen is thought to be a potential oral alternative for osteoarthritis treatment. The aim of this study was to evaluate the symptomatic efficacy of native type II collagen on joint pain and function, and its effects on urinary biological markers related to cartilage degeneration, in patients with knee osteoarthritis.

Materials and Methods

Patients

Patients aged between 45-70 years with the diagnosis of primary knee OA according to the American College of Rheumatology (ACR) criteria, Kellgren Lawrence radiological stage II or III and knee pain were included in the study. Exclusion criteria included intraarticular injections or physical therapy within the last year, a previous lower extremity surgery, oral treatment with glucosamine and/or chondroitin or other natural health products within the last month, synovitis and effusion in the knee, serious concomitant systemic diseases, peripheral or central neurological disorder, hypersensitivity to acetaminophen or severe cardiac, renal, hepatic or hematologic disease. The study was conducted at a single centre (Eskisehir Osmangazi University, Department of Physical Medicine and Rehabilitation, Eskisehir, Turkey), in full compliance with the amended Declaration of Helsinki, after obtaining approval from the institutional review board of Eskisehir Osmangazi University (date/no: 25-05-12/03). Informed consent was obtained from all patients prior to inclusion.

After a detailed anamnesis and physical examination, complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF) levels were measured and the tests of liver and kidney functions were performed in all patients included in the study. In addition, conventional standing anteroposterior (AP) and lateral knee radiographies were taken.

Study Design

The present study was designed as a randomized, single-blind (outcome assessors were blinded to the treatment allocation) and controlled clinical study with a three month follow-up period. Patients, who met inclusion/exclusion criteria, were selected from Outpatient Clinic between 2012 and 2013. Patients were randomly assigned to one of the two treatment groups using a computer generated random number list. All of the patients were assessed immediately at the beginning and at the end of the treatment.

Treatment Protocol

The AC group of patients (n=19) received 1500 mg/day of acetaminophen and the AC+CII group (n=20) received 1500 mg/day acetaminophen and 10 mg/day of native type II collagen (Bioiberica S.A., Spain) treatment for 3 months. No exercise program was given to patients. All patients were given information about not to force their knees while working or during other activities. During the study, patients' compliance to the treatment program was assessed by weekly phone calls.

Clinical and Biochemical Assessment

A blind physician unaware of the treatment allocation performed the clinical assessments at baseline, at the end of the treatment. The primary outcome measure of the study was the change from baseline in pain at rest and during walking, assessed from 0 (no pain) to 10 (worst possible pain) on a Visual Analogue Scale score (VAS) [15]. The secondary outcome measures were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [16], 20-m walking time and Short Form-36 (SF-36) [17]. Coll2-1, Coll2-1NO2 and Fibulin-3 levels were quantified in urine. 20-m walking time

was assessed with all patients walking on the same straight ground, and using the same standard words and the same chronometer. The WOMAC score consists of 24 items divided into 3 subscales: pain, stiffness and physical function. Global score has a range of 0 (no symptom) to 96 (worst symptoms), with standardized score to have a range of 0 to 100. With 36 items, the generic SF-36 questionnaire calculates 8 multi-item scales- physical functioning, physical role, emotional role, vitality, mental health, social role functioning, bodily pain, general health. Each scale ranges from 0 ("extreme symptoms/poor health") to 100 ("no symptoms/perfect health").

A sample of 6-7 mL of urine was taken twice from all patients, before and after the treatment period. After centrifugation of the urine, samples were collected and stored at -80°. Coll2-1 (it is obtained from triple helical structure of collagen type 2), Coll2-1NO2 (it is the nitrated form of Coll2-1) and Fibulin-3 (extracellular matrix protein) levels were determined in urine samples using a commercially available Enzyme-Linked Immuno Sorbent Assay (ELISA) kit (Artialis S.A., Liège, Belgium). Absorbance of the samples was read at 450 nm and the results were expressed as pM.

Statistical analysis

All data analyses were performed using Statistical Packages for the Social Sciences 21.0 (IBM SPSS Statistics; Armonk NY, USA) and SigmaStat 3.1. The descriptive data were represented with n (sample size), mean and standard deviation for continuous variables and, n (sample size), median and 25th and 75th percentiles for categorical variables. Normally distributed continuous measurements were compared across the groups by using t test. Score variables were compared between the groups with Mann-Whitney U test. Repeated measures analyses were performed with Repeated Measures ANOVA, based on one or more factors, evaluating the variables at different times of the units. Chi-square analyses were used for categorical variables. P value less than 0.05 ($p<0.05$) was considered significant.

Results

At the beginning of the study, "the only acetaminophen: AC" and "acetaminophen + native type II collagen combination group: AC+CII" groups consisted of 19 and 20 patients, respectively. Demographical characteristics of the patients did not differ significantly between the two groups (Table 1).

At baseline, there were no differences between the groups in clinical parameters, biochemical analysis and quality of life, except for VAS walking (p=*0.014*) and SF-36-Emotional Role (p=0.027) (Tables 2, 3). After 3 months of treatment, the patients of the AC+CII group reported significant improvements compared to baseline in pain, function and quality of life and as measured by VAS walking ($p<0.001$), WOMAC pain (p=0.003), WOMAC total (p=0.004), WOMAC physical functioning (p=0.016) and subscales of SF36 such as physical functioning (p=0.039), physical role (p=0.023), emotional role (p=0.048) and bodily pain (p=0.016). However in the AC group, only improvements in the quality of life survey were recorded within the subscales of SF36, physical functioning (p=0.002), emotional role (p=0.008), physical role (p=0.016), social role functioning (p=0.031) and VAS walking (p=0.024).

Table 1. Comparison of demographic characteristic of patients group

Parameter	Group AC (n=19)	Group AC+CII (n=20)	p
Age (years)	58.84±6.55	57.65±8.73	0.634
Gender			
Male	2	1	0.605
Female	17	19	
BMI (kg/m^2)	27.9±4.16	30.20±5.27	0.154
KGL scale			
Stage 2	18	16	0.342
Stage 3	1	4	
Disease duration (yr)	5.10±1.37	4.45±1.84	0.218

Data presented as mean ± SD
Group AC: Group Acetaminophen; Group AC + CII: Group Acetaminophen + Native Type II Collagen; BMI: body mass index

Comparisons between the groups revealed a significant difference in VAS walking score in favour of the AC+CII group as compared to AC group (p=0.002). A 50% reduction was registered in the AC+CII group. Biochemical markers of cartilage degradation in urine did not significantly improve in any of the groups ($p>0.05$) (Table 4).

Discussion

This randomized, single-blind, controlled trial was conducted to evaluate the effect of native type II collagen on knee OA when used concomitantly with acetaminophen. All in all, the addition of native type II collagen to a standard therapy with acetaminophen resulted in a clear benefit in terms of clinical improvement.

The aim of the OA treatment is to decrease the pain severity and functional limitation, as well as to slow the progression of the cartilage damage. Native type II collagen has been found to be effective in reducing arthritic pain in animal models [10-12] as well as in improving clinical outcomes in patients with rheumatoid arthritis [7-9]. However, few studies have evaluated the efficacy of native type II collagen in osteoarthritis [13, 14]. Crowley et al. [13] evaluated the effectiveness of native type II collagen as compared to glucosamine and chondroitin in patients with knee OA. Treatment with native type II colla-

Table 2. Inter and intra group comparisons of the clinical parameters

Parameter		Group AC (n=19)	Group AC+CII (n=20)	p	
VAS-rest	Pre-treatment	3 (0-8)	4 (0-9)	0.523	
	Post-treatment	3 (0-8)	2 (0-10)	0.665	
	p	0.727	0.141		
VAS-walking	Pre-treatment	3 (0-9)	6 (3-10)	0.014*	0.002**
	Post-treatment	3 (0-9)	3 (0-9)	0.469	
	p	0.024	p<0.001		
WOMAC-pain	Pre-treatment	9 (7-23)	12 (5-19)	0.471	
	Post-treatment	11 (5-23)	9 (5-17)	0.939	
	p	0.307	0.003**		
WOMAC-stiffness	Pre-treatment	5 (2-8)	4.5 (2-8)	0.904	
	Post-treatment	5 (2-8)	4 (2-10)	0.348	
	p	0.874	0.070		
WOMAC- physical function	Pre-treatment	33 (19-71)	37 (20-72)	0.895	
	Post-treatment	35 (17-70)	31 (17-65)	0.939	
	p	0.237	0.016*		
WOMAC - total	Pre-treatment	50 (28-103)	53.5 (29-98)	0.692	
	Post-treatment	52 (24-102)	44 (24-89)	p>0.05	
	p	0.248	0.004**		
		Group AC (n=19)	Group AC+CII (n=20)	p	
20 m. walking time (m/sn)	Pre-treatment	18.57±3.4	19.35±5.25	0.592	
	Post-treatment	18.84±4.79	18±3.49	0.553	
	p	0.728	0.084		

Data presented as median (25-75%), 20 m. walking time data presented as mean ± SD.
Group AC: Group Acetaminophen; Group AC + CII: Group Acetaminophen + Native Type II Collagen; VAS: Visual Analogue Scale; WOMAC: Western Ontario McMaster
*: p<0.05
**: p<0.005

gen (40 mg/d) was found to be more effective in reducing the WOMAC and VAS scores than glucosamine and chondroitin. Scarpellini et al. [14], compared the combination of glucosamine + chondroitin sulphate with or without native type II collagen (2 mg/day) in patients with OA of the knee, hand or hip. After 6 months and 1 year of treatment, clinical improvements were found in both groups, but differences between groups failed to reach statistical significance. In the present study, the addition of native type II collagen to a standard analgesic therapy resulted in significant improvement in joint pain (VAS walking scores), WOMAC scores (pain, physical function, total) and Short Form-36 (physical functioning, physical role, emotional role and bodily pain) as compared to baseline. However, intergroup comparisons only detected significant differences in pain during walking. The absence of differences in other clinical outputs could be attributed to the reduced sample size (n=39) and/or to the period of study (90 days).

Pain in walking is a common patient complaint in osteoarthritis that leads to loss of function and loss of daily living activities. To increase the functional status, walking pain should be reduced. Considering the effects of native type II collagen in walking pain, it may be an option in osteoarthritis to improve daily living activities.

Our study is different from other studies with dosage, mode of administration and combined agent. To our knowledge, this is the first study evaluating the efficacy of acetaminophen

Table 3. Inter and intra group comparisons of Short Form-36

Parameter		Group AC (n=19)	Group AC+CII (n=20)	p
SF-36 Physical functioning	Pre-treatment	75 (40-95)	75 (25-95)	p>0.05
	Post-treatment	85 (45-100)	77.5 (35-100)	0.610
	p	0.002**	0.039*	
SF-36 Physical role	Pre-treatment	0 (0-100)	0 (0-100)	0.365
	Post-treatment	0 (0-100)	62.5 (0-100)	0.599
	p	0.016*	0.023*	
SF-36 Emotional role	Pre-treatment	0 (0-100)	33.3 (0-100)	0.027*
	Post-treatment	33.3 (0-100)	66.6 (0-100)	0.412
	p	0.008**	0.048*	
SF-36 Vitality	Pre-treatment	65 (0-100)	47.5 (5-85)	0.243
	Post-treatment	65 (0-100)	42.5 (10-90)	0.285
	p	0.617	0.196	
SF-36 Mental health	Pre-treatment	56 (8-88)	70 (16-80)	0.481
	Post-treatment	56 (16-84)	66 (28-88)	0.463
	p	0.356	0.703	
SF-36 Social role functioning	Pre-treatment	100 (0-100)	100 (0-100)	0.722
	Post-treatment	100 (62.5-100)	100 (25-100)	0.062
	p	0.031*	0.172	
SF-36 Bodily pain	Pre-treatment	51 (10-74)	42 (10-72)	0.462
	Post-treatment	51 (10-100)	52 (10-84)	0.743
	p	0.520	0.016*	
SF-36 General health	Pre-treatment	67 (20-97)	60 (15-80)	0.339
	Post-treatment	57 (10-97)	62.5 (25-92)	0.592
	p	0.171	0.116	

Data presented as median (25-75%)
Group AC: Group Acetaminophen; Group AC + CII: Group Acetaminophen + Native Type II Collagen; SF-36: Short Form-36
*: p<0.05
**: p< 0.005

combined with native type II collagen. Acetaminophen is the first step in the treatment of osteoarthritis, and is known to be effective for the treatment of the symptoms of OA. Our results have showed that concomitant use of the native type II collagen improves its efficacy for the treatment of OA.

In the present study, urinary Coll2-1, Coll2-1NO2 and fibulin-3 levels were measured in order to assess the chondroprotective effects of native type II collagen. Collagen type 2 is the main component of the cartilage. Recent studies have demonstrated that urinary excretion of Coll2-1, which is obtained from triple helical structure of collagen type 2, and its nitrated form Coll2-1NO2, increases in patients with OA [18, 19]. Another new biomarker of cartilage damage is Fibulin-3, which in turn is derived from extracellular matrix proteins [20, 21]. These biomarkers are correlated with the severity of OA, but in our study, urinary levels of Coll2-1, Coll2-1NO2 and Fibulin-3 were not reduced in any of the studied groups. In the study of Scarpellini et al. [14] the clinical improvement in OA was associated to a decrease of the urinary levels of C-terminal cross-linked telopeptide type 2 collagen (CTX-2), indicating a slowing down of cartilage catabolism. The differences between studies could be explained by the nature of the biomarkers used, by differences on the time of follow up or by the combination with glucosamine + chondroitin which

Table 4. Inter and intra group comparisons of the biochemical parameters

Parameter		Group AC (n=19)	Group AC+CII (n=20)	p
Coll2-1 NO2	Pre-treatment	118.98 (8.98-722.11)	171.44 (25.16-596.13)	
	Post-treatment	130 (22.4-596.13)	155.25 (26.84-558.01)	0.989
	p	0.860	0.475	
Coll2-1	Pre-treatment	21.15 (14.92-73.08)	22.65 (16.06-32.05)	
	Post-treatment	22.93 (16.40-26.45)	21.75 (16.26-66.33)	0.503
	p	0.799	0.475	
Fibulin-3	Pre-treatment	18.56 (15.26-195.60)	27.8 (15.52-137.22)	
	Post-treatment	53.96 (17.04-137.22)	42.09 (16.42-349.16)	0.612
	p	0.738	0.206	

Data presented as median (25-75%)
Group AC: Group Acetaminophen; Group AC + CII: Group Acetaminophen + Native Type II Collagen

has been shown to prevent cartilage lost and decrease joint space narrowing in some studies [22, 23].

To our knowledge, this is the first study evaluating the effects of native type II collagen on cartilage degradation-related mediators as well as on quality of life when used concomitantly with acetaminophen. Limitations of the present study are small sample size and a short follow-up time. Chondroprotective and disease-modifying treatment modalities are still under investigation, despite considerable improvements have been achieved in the treatment of OA. Many new agents are being tested in pre-clinical trials but the results of the clinical studies are yet inadequate to draw a clear conclusion. Consequently, none of the disease-modifying drugs has been approved by FDA for the treatment of OA.

Native type II collagen is a new treatment and thought to be a potential option to prevent joint destruction, pain and loss of function by a mechanism of oral tolerance that avoids T-cells attack to collagen fibres in joints.

The results of the present trial do not show evidence that native type II collagen reduce cartilage destruction; however, it has been demonstrated that native type II collagen is effective in the symptomatic treatment of patients with knee osteoarthritis when used concomitantly with acetaminophen.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Eskişehir Osmangazi University (date/no: 25-05-12/03).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.B., O.A.; Design - F.B., O.A.; Supervision - O.A., M.O., F.T.; Materials - F.B.; Data Collection and/or Processing - O.A.; Analysis and/or Interpretation - O.B.; Literature Search - F.B.; Writing Manuscript - F.B., O.A.; Critical Review - F.B., O.A., M.O., F.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: Biochemical kits to analyse the degradation markers of type 2 collagen in urine were provided by Bioiberica S.A., Spain. Urine samples were analysed using these kits in the Biochemistry Laboratory, Eskisehir Osmangazi University. The study was designed and conducted independently by the authors. No funding was received for the collection, management, analyses, and interpretation of the data.

References

1. Felson DT, Zhang Y, Hannan MT, et al. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1995; 38: 1500-5. [CrossRef]
2. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol 2010; 6: 625-35. [CrossRef]
3. Evcik D, Babaoğlu ÜS. Osteoartrit Etyopatojenezi. Sarıdoğan M (Editor). Tanıdan Tedaviye Osteoartrit. İstanbul: Nobel Tıp Kitapevleri; 2007; 51-72.
4. Meulenbelt I, Kloppenburg M, Kroon HM, et al. Urinary CTX-II levels are associated with radiographic subtypes of osteoarthritis in hip, knee, hand, and facet joints in subject with familial osteoarthritis at multiple sites: the GARP study. Ann Rheum Dis 2006; 65: 360-5. [CrossRef]
5. Trentham DE, Halpner A, Trentham R, Bagchi M, Kothari S, Preuss HG et al. Treatment of rheumatoid arthritis using undenatured type II collagen. Original Internist 2002; 9: 12-5.
6. Bagchi D, Misner B, Bagchi M, et al. Effects of orally administered undenatured type II collagen against arthritic inflammatory diseases: a mechanistic exploration. Int J Clin Pharmacol Res 2002; 22: 101-10.

7. Barnett ML, Kremer JM, St. Clair EW, et al. Treatment of rheumatoid arthritis with oral type II collagen. Results of a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum 1998; 41: 290-7. [CrossRef]
8. Ausar S, Beltramo D, Castagna L, et al. Treatment of rheumatoid arthritis by oral administration of bovine tracheal type II collagen. Rheumat Internat 2001; 20: 138-44. [CrossRef]
9. Wei W, Zhang LL, Xu JH, et al. A multicenter, double-blind, randomized, controlled phase III Clinical trial of chicken type II collagen in rheumatoid arthritis. Arthritis Res Ther 2009; 11: 180. [CrossRef]
10. Gupta RC, Bagchi D, Skaggs P, et al. Therapeutic efficacy of undenatured type-II collagen (UC-II) in comparison to glucosamine and chondroitin in arthritic horses. J Vet Pharmacol Ther 2009; 32: 577-84. [CrossRef]
11. Deparle LA, Gupta RC, Canerdy TD, et al. Efficacy and safety of glycosylated undenatured type-II (UC-II) collagen in therapy of arthritic dogs. J Vet Pharmacol Ther 2005; 28: 385-90. [CrossRef]
12. Mannelli LDC, Micheli L, Zanardelli M, Ghelardini C. Low dose native type II collagen prevents pain in a rat osteoarthritis model. BMC Musculoskelet Disord 2013; 14: 228. [CrossRef]
13. Crowley DC, Lau FC, Sharma P, et al. Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial. Int J Med Sci 2009; 6: 312-21. [CrossRef]
14. Scarpellini M, Lurati A, Vignati G, et al. Biomarkers, type II collagen, glucosamine and chondroitin sulfate in osteoarthritis follow-up: the "Magenta osteoarthritis study" J Orthopaed Traumatol 2008; 9: 81-7. [CrossRef]
15. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med 2001; 38: 633-8. [CrossRef]
16. Tüzün EH, Eker L, Aytar A, Daşkapan A, Bayramoğlu M. Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. Osteoarthritis Cartilage 2005; 13: 28-33. [CrossRef]
17. Koçyiğit H. Aydemir Ö, Fişek G. Kısa form-36(KF-36)'nın Türkçe versiyonunun güvenirliliği ve geçerliliği. İlaç ve Tedavi Dergisi 1999; 12: 102-6.
18. Huebner JL, Williams JM, Deberg M, Henrotin Y, Kraus VB. Collagen fibril disruption occurs early in primary guinea pig knee osteoarthritis. Osteoarthritis Cartilage 2010; 18: 397-405. [CrossRef]
19. Deberg MA, Labasse AH, Collette J, Seidel L, Reginster JY, Henrotin YE. One-year increase of Coll 2-1, a new marker of type II collagen degradation, in urine is highly predictive of radiological OA progression. Osteoarthritis Cartilage 2005; 13: 1059-65. [CrossRef]
20. Kobayashi N, Kostka G, Garbe JH, et al. A comparative analysis of the fibulin protein family. Biochemical characterization, binding interactions, and tissue localization. J Biol Chem 2007; 282: 11805-16. [CrossRef]
21. Deberg M, Dubuc JE, Labasse A, et al. One-year follow-up of Coll2-1, Coll2-1NO2 and myeloperoxydase serum levels in osteoarthritis patients after hip or knee replacement. Ann Rheum Dis 2008; 67: 168-74. [CrossRef]
22. Pavelká K, Gatterová J, Olejarová M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002; 162: 2113-23. [CrossRef]
23. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001; 357: 251-6. [CrossRef]