

## Short-Term Efficacy of Intraarticular Hyaluronic Acid Injection in Gonarthrosis

Gonartrozda İntra-artiküler Hyalüronik Asid Enjeksiyonunun Kısa Dönem Etkinliği

Nilay Şahin<sup>1</sup> , Serdar Sargin<sup>2</sup> , Fatih Çeşme<sup>3</sup> , Demirhan Dıraçoğlu<sup>4</sup> , Cihan Aksoy<sup>4</sup> 

1 Physical Medicine and Rehabilitation Department, Balıkesir University Medicine of Faculty, Balıkesir/Turkey

2 Orthopaedics and Traumatology Department, Balıkesir University Medicine of Faculty, Balıkesir/Turkey

3 Physical Medicine and Rehabilitation Department, Corlu Vatan Hastanesi, Corlu, Tekirdağ/Turkey

4 Physical Medicine and Rehabilitation Department, Istanbul University, Istanbul Faculty of Medicine, Istanbul/Turkey

### ÖZET

**AMAÇ:** Gonartroz, ağrı ve sertliğe neden olan kronik, dejeneratif bir hastalıktır. Konservatif ve cerrahi olarak tanımlanan birçok tedavi yöntemi vardır. Eklem içi hyaluronik asit enjeksiyonu bu yöntemlerden biridir. Tedavide rutin olarak kullanılan farklı preparatlar vardır ve hangisinin daha etkili olduğuna dair net bir kanıt yok. Farklı molekül ağırlıklarına sahip HA preparatlarının gonartrozu olan hastaların ağrı ve işlevselliği üzerine etkilerini araştırmayı amaçladık.

**GEREÇ VE YÖNTEM:** İki taraflı gonartroz tanısı konan 55 hastanın 30'u (40-80 yaşları arasında) çalışmaya alındı. Hastalar rastgele 3 gruba ayrıldı (Hyalgan (N = 10), Ortez (N = 10), Synvisc (N = 10)). Hastalar tedaviden önce ve sonra değerlendirildi. Klinik muayene, Görsel Analog Skala, WOMAC skoru, sertlik ve fiziksel durum, 15 m yürüme süresi ve 15 basamak yukarı ve aşağı performans değerlendirildi.

**BULGULAR:** Gruplar arasında yaş, vücut kitle indeksi (BKI) ve semptom süresi açısından anlamlı fark yoktu (sırasıyla p: 0.917, p: 0.721, p: 0.519). Her üç grupta da tedavi öncesi VAS skorları (hareket, dinlenme ve gece) tedaviden sonra anlamlı olarak azaldı (p=0.001). WOMAC sonuçlarına göre tedaviden sonra ağrı, sertlik belirgin olarak azaldı (p=0.001). Herhangi bir parametrede gruplar arasında anlamlı fark bulunmadı (p=0.05).

**SONUÇ:** Bu çalışmanın sonuçları, WOMAC ve VAS skorlarındaki HA preparatları arasında istatistiksel olarak anlamlı bir fark olmadığını ortaya koydu; Bununla birlikte, HA'nın etkili olduğu ve erken evre gonartroz tedavisinde kullanılması gerektiği bulunmuştur.

**Anahtar Kelimeler:** hyaluronik asit, enjeksiyon, Gonartroz, Moleküler ağırlık

### ABSTRACT

**OBJECTIVE:** Gonarthrosis is a chronic, degenerative disease that causes pain and stiffness. There are many treatment methods defined as conservative and surgical. Intra-articular hyaluronic acid injection is one of these methods. There are different preparations routinely used in the treatment. There is no clear evidence of which is more effective. We aimed to investigate the effectiveness of HA preparations with different molecular weights on pain and functionality of patients with gonarthrosis.

**MATERIALS AND METHODS:** 30 of 45 patients (ranging 40-80 years old) diagnosed as bilateral gonarthrosis were enrolled in the study. Patients were randomly divided into 3 groups (Hyalgan (N = 10), Orthovics (N = 10), Synvisc (N = 10)). Patients were evaluated before and after treatment. Clinical examination, Visual Analogue Scale, WOMAC score, stiffness and physical condition, 15 m walking time and 15 steps up and down performance were evaluated.

**RESULTS:** There was no significant difference between the groups in terms of age, body mass index (BMI) and symptom duration (p: 0.917, p: 0.721, p: 0.519, respectively). In all three groups, pre-treatment VAS scores (motion, rest and night) significantly decreased after treatment (p <0.001). According to WOMAC results, pain, stiffness decreased significantly after treatment (p <0.001). There was no significant difference between the groups in any parameter (p > 0.05)..

**CONCLUSION:** The results of this study revealed no statistically significant difference between HA preparations in WOMAC and VAS scores; However, HA has been found to be effective and should be used in the treatment of early stage gonarthrosis.

**Keywords:** hyaluronic acid, injection, gonarthrosis, molecular weight, efficacy

## INTRODUCTION

Gonarthrosis is a chronic, degenerative disease that causes pain and stiffness as a result of the breakdown of articular cartilage. The estimated prevalence of gonarthrosis, which increases with age, is 24% in the general adult population (1). The main goal in the treatment of gonarthrosis is to provide functional improvement by reducing pain (2). There are many treatment methods defined as conservative and surgical (3). Intra-articular hyaluronic acid (HA) injection, one of these methods, has been shown to be effective in controlling the signs and symptoms of the disease. In today's world for the painful knees, whether or not radiologically detected arthrosis, especially intra-articular injection of HA is one of the treatment methods preferred by physicians (4).

HA is a glycosaminoglycan commonly found in cartilage, synovial fluid, skin and anterior chamber fluid in the eye. The decrease in molecular size and concentration of HA is thought to be acceleration of the progression to osteoarthritis (5). In gonarthrosis, the rheological properties of synovial fluid are decreased with joint cartilage damage. The viscoelastic properties of HA are responsible for some of the protective functions of synovial fluid. The function of HA in the joint is to regulate biochemical processes, shock absorption and lubrication (6). HA has been shown to have various effects on cells in vitro. These effects are reducing leukocyte count and interleukin-1-induced prostaglandin synthesis, stabilizing lysosomal membranes, inhibiting phagocytosis and chemotaxis of inflammatory cells, and removing free radicals and other reactive oxygen species (7). Therefore; HA injection appears to be a viable solution supported by clinical evidence by improving viscous properties (8).

HA can be divided into three groups based on molecular weight: low molecular weight ( $0.5$  to  $1 \times 10^6$  dalton (Da)), medium molecular weight ( $2 \times 10^6$  Da) and high molecular weight ( $6 \times 10^6$  (Da)) (9). There are different HA preparations (molecular weight, dosage, etc.) routinely used in the treatment, and there is no clear evidence of which is more effective. In this study, we aimed to investigate the effectiveness of HA preparations with different molecular weights on pain and functionality of patients with gonarthrosis.

## MATERIALS & METHOD

Forty five patients (ranging between 40 and 80 years old) diagnosed as bilateral gonarthrosis according to the American College of Rheumatology (ACR) criteria (10) suffering from pain and limitation of motion were enrolled in the study. All patients were classified according to the radiological evaluation of Kellgren and Lawrence (11) on the anteroposterior and lateral radiographs. Grade 2 and 3 patients were included in the study. Thirty patients with primary gonarthrosis who did not benefit from 1st and 2nd stage medical therapies and accepted intra-articular injection were included in the study.

Patients with Severe knee trauma, secondary osteoarthritis, signs of inflammation such as knee effusion, knee joint redness and heat increase, knee ligament damage, any orthopedic intervention in the last six months, any intra-articular knee injection in the last six months, or lumbar and hip pathologies and comorbidity were excluded from the study. After explaining the injection procedures to all cases, written informed consent of the patients was received. Local ethical committee approval was obtained.

Patients were included in the study according to the following criteria:

- 40-80 years of age
- Knee pain lasting more than 6 months
- Stage 2-3 according to Kellgren-Lawrence (KL) classification in radiological evaluation (11).
- Has not benefited from stage 1-2 medical treatments
- No other pathology that can cause knee pain
- No surgical intervention for the knee
- Lack of any pathology of the waist or hip
- No knee injections in the last 6 months
- Participating voluntarily in the study.

### **Randomization:**

45 patients who met the inclusion and exclusion criteria were eligible for the study. 11 of these patients who did not accept injection treatment were excluded from the study and four patients were excluded from the study due to additional health problems on the day of injection. As a conclusion, Thirty patients whose names were written on non-opaque envelopes were randomly divided into three groups in a 1: 1: 1 ratio, after a physical examination. The

study was completed with 30 patients who were treated and followed up completely.

These 30 patients were randomly divided into 3 groups of 10 patients. In the first group (N = 10) low molecular weight Hyalgan, in the second group (N = 10) medium weight Orthovics and in the third group (N = 10) high molecular weight Synvisc was applied intraarticularly. The injections were administered once a week for a total of three times. The patients were informed about the procedure and complications before the injection. The injections were administered by the same physician. Patients were evaluated by another physician who was unaware of the treatment groups after six months.

Povidone iodine solution was used for asepsis. Chlorhexidine was also used for the patients with povidone iodine allergy. The injector needle was inserted into the joint from the superolateral of the patella. Firstly, if there was effusion in the knee, it was aspirated. HA was then injected without removing the syringe needle. Isometric quadriceps strengthening exercise program was started for each group besides injection. Exercise program was performed under the control of physiotherapist. Each patient was told to take simple analgesics (paracetamol) depending on the pain.

#### **Evaluation Criteria's:**

Demographic data of the patients were recorded. Laboratory and radiological examinations of the patients were examined. The causes of secondary gonarthrosis were investigated. The patients were diagnosed by the same doctor. Gonarthrosis was diagnosed according to ACR criteria.

Patients were evaluated before and after treatment. Clinical examination, Visual Analogue Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (12), stiffness and physical condition, 15 m walking time and 15 steps up and down performance were evaluated. The patient and the doctor were blinded according to the type of injection.

1. Pain assessment: Patients' knee pain during daily activities and at rest was assessed by visual analogue scale

(VAS). It was scored between 0 and 10 (0: no pain, 10: severe pain) (13).

2. Disability and Quality of Life Measurements: Functional status was assessed by WOMAC. (12) In addition, 15 m walking time and 15 steps up and down time were evaluated and recorded.

#### **Statistical Analyses:**

SPSS 20.0 software was used for statistical analysis. In addition to descriptive statistical methods, Wilcoxon test was used for repetitive measurements of three groups, Mann-Whitney-U test was used for independent comparison of three groups, and Fisher Chi-Square test was used for comparing qualitative data. The results were evaluated at p <0.05 significance level and 95% confidence interval

#### **RESULTS**

The average age of the patients in the treatment groups was 43-76 (mean 60.7 years). There was no significant difference between the groups in terms of age, body mass index (BMI) and symptom duration (p: 0.917, p: 0.721, p: 0.519, respectively) (Table 1). Demographic data of all three groups are shown in Table 1.

**Table 1.** Demographic findings of the patients included in the study. BMI body mass index, F female, M male

PARAMETER	Low (Hyalgan) (n:10) Mean±SD	Medium (Orthovisc) (n:10) Mean±SD	High (Synvisc) (n:10) Mean±SD	P Value
Gender (F/M)	8/2	9/1	8/2	
Radiological grade (%)				
II	6	6	5	
III	4	4	5	
Age (Year)	59,9±3,4	60,6±2,9	61.6±2,1	0,917
BMI(kg/ m <sup>2</sup> )	28,61±1,39	30,31±1,85	30,4±1,95	0,721
Symptom duration (months)	21±5,02	27,4±5,3	20,2±3,9	0,519

**Table 2.** Pre-and post-injection evaluation results in all 3 groups

	Low (Hyalgan) n: 10			Medium (Orthovisc) n:10			High (Synvisc) n:10		
	Pre-injection	Post-injection	p value	Pre-injection	Post-injection	p value	Pre-injection	Post-injection	p value
<b>Flexion</b>	125,41	130,41	0,041	116,66	129,44	0,026	124,44	131,66	0,026
<b>VAS-Rest</b>	4,33	2,50	0,004	3,44	1,55	0,027	3,55	2,22	0,016
<b>VAS-Movement</b>	6,66	5,25	0,006	6,88	4,66	0,011	5,88	4,66	<b>0,079</b>
<b>VAS-Night</b>	3,33	1,91	0,004	2,00	0,77	<b>0,109</b>	2,88	2,11	<b>0,288</b>
<b>15 m walking</b>	19,75	14,41	0,004	18,66	14,33	<b>0,084</b>	15,77	13,00	0,027
<b>Step up and down</b>	25,75	21,16	0,007	28,55	21,44	0,012	26,00	21,88	0,007
<b>WOMAC -Pain</b>	4,64	3,46	0,024	4,94	3,61	<b>0,109</b>	4,46	3,32	<b>0,080</b>
<b>WOMAC-Stiffness</b>	4,02	2,85	0,017	5,15	2,08	0,018	3,66	1,61	0,017

In all three groups, pre-treatment VAS scores (motion, rest and night) significantly decreased after treatment ( $p < 0.001$ ). Knee joint range of motion was found to be significantly increased after treatment ( $p < 0.001$ ). There was a significant decrease in 15-meter walk and 15-step up and down times after treatment ( $p < 0.005$ ). According to WOMAC results, pain, stiffness and physical condition decreased significantly after treatment ( $p < 0.001$ ) (Table 2). There was no significant difference between the groups in any parameter ( $p > 0.05$ ).

## DISCUSSION

Intraarticular HA injection is a commonly used treatment to relieve symptoms in gonarthrosis (14). HA injections have the potential to delay the need for arthroplasty (15). Injections as recommended by ACR and OARSI are used as a secondary treatment for patients with gonarthrosis who are unresponsive to medical treatment. In this study, the efficiency of three different molecular weight HA preparations (LMW (Hyalgan), MMW (Orthovisc) and an HMW (Synvisc)) in the treatment of gonarthrosis was compared. As a result, we found significant improvement in short-term results in terms of pain, stiffness, range of motion and physical condition with the injection treatment independent from type of HA preparations. All of the

groups did not show any difference in WOMAC or VAS scores at any time after treatment during follow-up time. Also, during treatment no complication occurred in all groups. Thus, we concluded that these three forms of HA are comparable with no significant adverse event. Our results point that all three HA preparations can improve joint function and relieve pain shortly after completion of treatment and this result can last for at least six month. We can conclude that HA treatment options are equally effective in managing symptoms in patients with gonarthrosis.

These results are in accordance with previous reports. A meta-analysis made by Wang reported that intra-articular injection of HA was effective and safe for treating patients with gonarthrosis, as it resulted in decreased pain and functional improvement of the joint (16). Compared to placebo, in another trial conducted by Bellamy, HA was more effective in improving pain and function measured with WOMAC and VAS scores (17).

The existence of HA with different molecular weight raises questions as to which preparation is better for patients with knee OA. The effectiveness of HA injections depends on molecular weight, dose and frequency of administration. The concentrations of the preparations used in

viscosupplementation are similar. Therefore, the differences between the rheological properties of these preparations depend on their molecular weight rather than their concentration (18). The molecular weight of the HA product has been shown to correlate with clinical outcomes (19). We used an LMW(Hyalgan), MMW(Orthovics) and an HMW(Synvics) preparation according to manufacturer's instructions.

Today, intraarticular HA preparations with different molecular weights have been used widely in the treatment of OA. Several investigations and meta-analyses have been conducted on different molecular weight HAs in the past years and different results have been reported. The differences between HA preparations, especially between high molecular weight and low molecular weight HA, are still controversial. Some clinical studies have reported increased efficiency of high molecular weight HA products compared to LMW HA (20-23). Also in the meta-analysis study, products with a molecular weight of 3000 kDa have been shown to exhibit more favorable results in terms of both efficiency and safety than those with lower molecular weight (19). Wang and friends found significant improvements in pain and functional outcomes with few adverse events. They also found that the patients over sixty-five years of age and those with the most advanced radiographic stage of osteoarthritis (complete loss of joint space) were less likely to benefit from intra-articular injection of hyaluronic acid (24). In the meta-analysis conducted by Lo GH and friends, Studies with seven different HA preparations were examined and it was found that high molecular weight HA preparations were more effective than low molecular weight HA preparations (25). It was emphasized that interpretation of these results is difficult due to heterogeneity between studies.

Our results are supported by most of the trials published comparing different HA according to their molecular weight. In another systematic review and meta-analysis by Arrich J and friends, On the contrary, no difference was found between HA preparations in terms of molecular weight and effects (26). Karlsson and friends declared clinical improvement during the first 26 weeks of treatment in two groups of patients treated with HA intra-articular injection, either HMW or LMW, but no difference between the two groups was found during one-year follow-up (27).

By Kotevoglou and friends, during a six-month period, patients treated with either HMW HA, LMW HA or placebos were evaluated using WOMAC score. Placebo was proved to be inferior to HA treatment. However, no clear benefit was found for either HA (5).

With a molecular weight of  $6 \times 10^6$  Da, the elastoviscous properties of Hylan GF 20 (Synvisc) are similar to the synovial fluid properties of healthy young adults (5). When compared with control saline injections or arthrolysis, it was found to be reliable and statistically superior in efficiency (28). The viscoelastic properties of hyaluronan (Orthovisc) are lower than that of hyaluronan (molecular weight  $1.55 \times 10^6$  Da) in normal healthy synovial fluid. Electrophysiological studies in Hylan-treated animals have shown that high molecular weight preparations have an analgesic effect (29). Animal studies have shown that as the molecular weight of HA preparations increases (hyaluronan or hylan), cartilage production increases (30).

The main limitations of this study are; low number of cases, absence of placebo group and long-term follow-up.

## CONCLUSION

Currently, intraarticular HA injections are substantially different in their intrinsic properties and characteristics. The results of this study revealed no statistically significant difference between HA preparations in WOMAC and VAS scores; However, HA has been found to be effective and should be used in the treatment of early stage gonarthrosis. We concluded that intra-articular hyaluronic acid administration significantly improved pain, stiffness, range of motion and physical condition in patients with gonarthrosis in whom 1st and 2nd medical treatment was inadequate.

Yazarlar arasında çıkar çatışması yoktur.

The author declares no conflict of interest.

Finansal Destek: yoktur / Funding : none

doi: <https://doi.org/10.33713/egedbd.588375>

## REFERENCE

1. Pereira D, Peleteiro B, Araujo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthritis Cartilage*. 2011;19:1270-85.

2. Bennell KL, Hinman RS, Metcalf BR, Buchbinder R, McConnell J, McColl G, et al. Efficacy of physiotherapy management of knee joint osteoarthritis: a randomised, double blind, placebo controlled trial. *Ann Rheum Dis.* 2005;64:906-12.
3. Pagnano M, Westrich G. Successful nonoperative management of chronic osteoarthritis pain of the knee: safety and efficacy of retreatment with intra-articular hyaluronans. *Osteoarthritis Cartilage.* 2005;13:751-61.
4. Oliveira MZ, Albano MB, Namba MM, da Cunha LA, de Lima Goncalves RR, Trindade ES, et al. Effect of hyaluronic acids as chondroprotective in experimental model of osteoarthritis. *Rev Bras Ortop.* 2014;49:62-8.
5. Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. *Rheumatol Int.* 2006;26:325-30.
6. Bashaireh K, Naser Z, Hawadya KA, Sorour S, Al-Khateeb RN. Efficacy and safety of cross-linked hyaluronic acid single injection on osteoarthritis of the knee: a post-marketing Phase IV study. *Drug Des Devel Ther.* 2015;9:2063-72.
7. Tasciotoaglu F, Oner C. Efficacy of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis. *Clin Rheumatol.* 2003;22:112-7.
8. Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. *ORTHOVISC Study Group. Clin Orthop Relat Res.* 2001;130-43.
9. de Rezende MU, de Campos GC. Viscosupplementation. *Rev Bras Ortop.* 2012;47:160-4.
10. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum.* 1986;29:1039-49.
11. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis.* 1957;16:494-502.
12. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol.* 1988;15:1833-40.
13. Frank A, Moll J, Hort J. A comparison of three ways of measuring pain. *Rheumatology.* 1982;21:211-7.
14. Monticone M, Frizziero A, Rovere G, Vittadini F, Uliano D, S LAB, et al. Hyaluronic acid intra-articular injection and exercise therapy: effects on pain and disability in subjects affected by lower limb joints osteoarthritis. A systematic review by the Italian Society of Physical and Rehabilitation Medicine (SIMFER). *Eur J Phys Rehabil Med.* 2016;52:389-99.
15. Karatosun V, Unver B, Gocen Z, Sen A. Comparison of two hyaluronan drugs in patients with advanced osteoarthritis of the knee. A prospective, randomized, double-blind study with long term follow-up. *Clin Exp Rheumatol.* 2005;23:213-8.
16. Miltner O, Schneider U, Siebert CH, Niedhart C, Niethard FU. Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis--a prospective clinical trial. *Osteoarthritis Cartilage.* 2002;10:680-6.
17. Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. *J Rheumatol.* 2006;33:951-6.
18. Adams ME, Lussier AJ, Peyron JG. A risk-benefit assessment of injections of hyaluronan and its derivatives in the treatment of osteoarthritis of the knee. *Drug Saf.* 2000;23:115-30.
19. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E. Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of the Knee. *Am J Sports Med.* 2016;44:2158-65.
20. Raman R, Dutta A, Day N, Sharma HK, Shaw CJ, Johnson GV. Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the treatment of osteoarthritis of the knee -- a prospective randomized clinical trial. *Knee.* 2008;15:318-24.
21. Özkılıç R, Kuru T, İpek S, Keskin E, Işık C, Kaya YE. Diz Osteoartritinde İntraartiküler Hyalüronik Asit ve Tenoksikamın Ağrı ve Diz Eklem Fonksiyonları Üzerine Etkilerinin Karşılaştırılması. *Acta Med Alanya* 2018;2(3):149-58.
22. Atamaz F, Kirazli Y, Akkoc Y. A comparison of two different intra-articular hyaluronan drugs and physical therapy in the management of knee osteoarthritis. *Rheumatol Int.* 2006;26:873-8.
23. Berenbaum F, Grifka J, Cazzaniga S, D'Amato M, Giacobelli G, Chevalier X, et al. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. *Ann Rheum Dis.* 2012;71:1454-60.
24. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am.* 2004;86-A:538-45.
25. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA.* 2003;290:3115-21.
26. Arrich J, Piribauer F, Mad P, Schmid D, Klaushofer K, Mullner M. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. *CMAJ.* 2005;172:1039-43.
27. Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology (Oxford).* 2002;41:1240-8.
28. Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin Ther.* 1998;20:410-23.
29. Wobig M, Bach G, Beks P, Dickhut A, Runzheimer J, Schwieger G, et al. The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a

comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. Clin Ther. 1999;21:1549-62.

**30.** Rydell N, Balazs EA. Effect of intra-articular injection of hyaluronic acid on the clinical symptoms of osteoarthritis and on granulation tissue formation. Clin Orthop Relat Res. 1971;80:25-32.