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ORIGINAL ARTICLE

Combining two hyaluronic acids in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial

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Abstract Synovial fluid in patients may differ in molecular weight depending on the presence and degree of osteoarthritis. Treatment is not directed at this relationship. Patients with osteoarthritis of the knee with resting visual analogue scale (VAS) pain of >45 mm were included in a randomized, prospective, double-blind cohort followed for 16 weeks. Patients were randomized at baseline to receive a three intra-articular injection series with one of: dual molecular weight (DMW; 580–780 kDa+1.2 to 2.0 million Da); low molecular weight (LMW; 500–730 kDa); high molecular weight (HMW; 6 million Da); or saline placebo over 3 weeks. Patients completed baseline assessment of rest and walking VAS pain (primary efficacy variable), collection of a 5-point categorical global satisfaction score, and record of adverse events. Two-hundred and twenty-five patients (age 68±8 y) were screened and 200 were randomized to one of the four groups. There were no differences at baseline between groups. At 4, 12 and 16 weeks, respectively, walking VAS pain was significantly improved in all treatment groups vs. placebo: DMW (79.6%, $p<0.001$; 85.6, $p<0.001$; 89.3%, $p<0.001$); LMW (73.6%, $p<0.001$; 76.4, $p<0.001$; 81.3%, $p<0.001$) and HMW (69.1%, $p<0.001$; 81.0, $p<0.001$; 79.1%, $p<0.001$). Patients in the DMW group had significantly greater improvement ($p<0.007$) in VAS walking pain by 3 weeks (following the second injection) compared to all groups. This difference was persistent at 16 weeks. Greater improvement in patients who received the DMW product was achieved by the second injection persistent at 16 weeks.

Keywords Hyaluronic acid · Knee osteoarthritis · Molecular weight composition

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Introduction

Hyaluronic acid (HA) is an unbranched high-molecular-weight polysaccharide distributed throughout the body, especially as a major component of the synovial fluid and of cartilage. The primary role of the HA in synovial fluid and cartilage is to maintain the viscoelastic structural and functional characteristics of the articular matrix. Osteoarthritis (OA) is the result of mechanical and biological events that destabilize the normal degradations synthesis of articular cartilage [1] and is characterized by a decrease in the concentration and molecular weight of HA, which in turn may lead to the hallmark signs of pain and loss of function in weight-bearing joints such as the knee [2]. Hence, intra-articular viscosupplementation with HA may restore the concentration and molecular weight characteristics in the articular matrix, resulting in improved pain control and function [3].

Intra-articular HA is indicated currently for use in patients who may not have responded to a program of non-pharmacological therapy and pain control with analgesics including acetaminophen [4]. Clinical trials of intra-articular HA preparations have shown pain relief significantly greater than those who injected with placebo [5–8] and comparable or superior to intra-articular glucocorticoids [9, 10]. Al-

though pain relief is achieved more slowly with HA preparations than with intra-articular glucocorticoid injections, the effect may last considerably longer. Similarly, intra-articular HA has shown comparable improvement in pain with oral anti-inflammatory preparations [11]. Recent metanalyses have shown effect sizes of intra-articular corticosteroid and hyaluronic acid of variable molecular weight to be similar [9, 12]; hence, physicians have further support to consider the attributes of HA for treatment along the continuum from early to advanced osteoarthritis [3, 13].

Several HA compounds are currently utilized worldwide by clinicians which differ in molecular weight composition, dosing regimens, and claims of efficacy. Specifically, it is unclear whether differences in efficacy are found among products [12, 14, 15] while patients receive specific products without any objective criteria for a given choice. It has been described that differences in HA molecular weight and concentrations in the synovial fluid occur among adults with a shift in the elastic to viscous ratio in osteoarthritis that is consistent with the degree of severity and character of symptoms [2]. The knee in dynamic motion requires elastic composition at optimal molecular weight (MW) in balance with viscous needs. For example, high-frequency loading through synovial fluid is dissipated through a dynamic change in hyaluronic acid toward more elastic modulus compared to more viscous properties when the load to hyaluronic acid is of low frequency [2]. While a given HA product has a limited range of molecular weight typically low, medium, or high, no product has been designed to provide a complement of composition that mimics the needs of the active osteoarthritic knee joint. These attributes may promote a more beneficial rheological environment in the osteoarthritic joint [16].

We are unaware of any other published studies that have prospectively followed patients who were administered HA of combined lower and higher MW. Hence, the purpose of this study was to evaluate the clinical outcomes of pain at rest and following walking activity as well as adverse events, the use of concomitant therapeutic modalities and patient satisfaction following randomization to one of intra-articular viscosupplementation with a lower (500–730 kDa), higher (6 million Da), or combined lower and higher MW (dual molecular weight (DMW)) hyaluronic acid in osteoarthritis of the knee.

Materials and methods

Subjects

Patients were recruited consecutively from three independent sites in a large primary care referral center in Ontario, Canada. From these referral sources, patients who were prescribed a series of three weekly HA injections to control symptoms were randomized to receive one of three HA compositions: lower molecular weight (LMW) HA, higher molecular weight (HMW), combined lower and higher molecular weight and different concentrations (DMW) or saline placebo. Randomization was done using a computer-generated random number table. Physicians and patients were blinded to assignment (syringes were covered to conceal any details of product or volume).

At entry, all patients had, in the index knee, radiographic evidence of grade 1 to 3 medial compartment osteoarthritis [17], did not exhibit non-arthritis-related disease, and gave consent as approved by the University of Western Ontario ethics review board. Other exclusion criteria included: end-stage OA or previous use of intra-articular corticosteroid or HA within the previous 6 months. The study was funded in part by the Canadian Institutes of Health Research.

Assessment

Baseline assessment included demographic data (age, gender, body mass index, comorbidities and concomitant medications). All patients qualified for prescription of intra-articular HA injection based on history of unilateral knee pain and disability, radiographic evidence of osteoarthritis (as above), and a visual analogue scale (VAS) non-weight-bearing seated rest pain score of at least 45 mm out of 100 mm. Patients could refuse this treatment and hence were not followed. Outcome measures included those recommended previously [18, 19].

The primary efficacy variable was improvement in self-paced 40-m walking pain VAS [7]. Secondary outcomes included improvement in seated rest pain VAS, patient global satisfaction using a 5-point numerical scale, presence of adverse events, and concomitant medications.

Assessments were conducted at baseline V1, and prior to each injection at visits 2, 3 and 4, and follow-up visits at 4 (V5) weeks, 12 (V6) weeks, and 16 (V7) weeks (Fig. 1).

Intervention

Low molecular weight solution of HA was a marketed product of $0.50–0.73 \times 10^6$ Da and the high molecular weight HA was a marketed product of 6 million kDa, both indicated for intra-articular injection for knee osteoarthritis. Two milliliters of LMW and HMW were injected using an aseptic technique and a medial approach. No anesthetic was used either topically or intra-articularly. Each injection (three) was performed 1 week apart (±2 days) by an experienced clinician. All injections were initiated after baseline and follow-up assessments of VAS and global satisfaction which were performed by an independent technician. The DMW preparation consisted of 0.7 ml of sterile 2.2% LMW ($0.58–0.78 \times 10^6$ Da) sodium hyaluro-

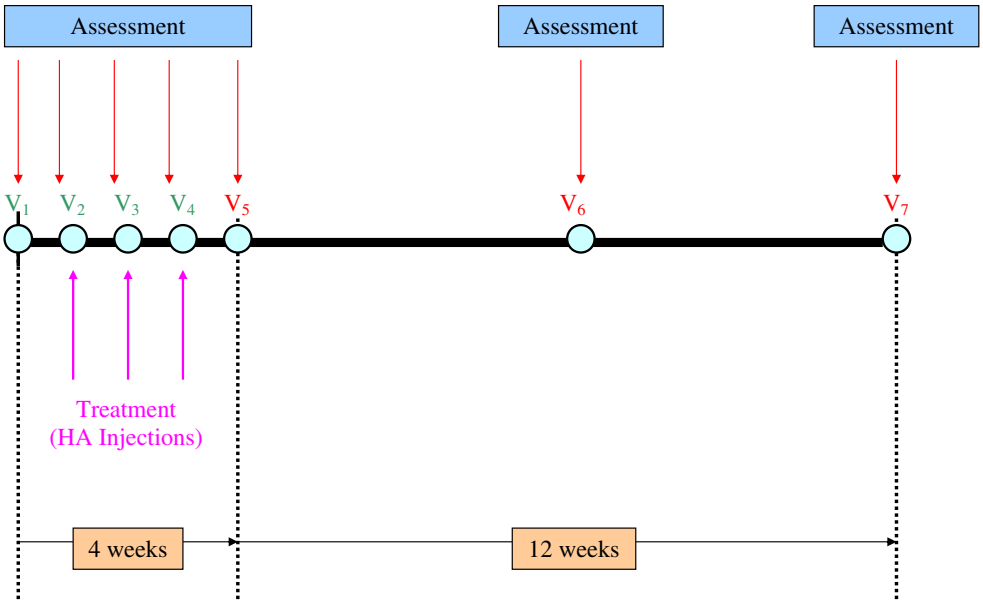

Fig. 1 Time scale of clinical trial

Key: V_1 = Visit 1, V_2 = Visit 2, V_3 = Visit 3, V_4 = Visit 4, V_5 = Visit 5, V_6 = Visit 6, V_7 = Visit 7

nate and 0.7 ml of sterile 1% HMW ($1.2–2.0\times10^6$ Da) sodium hyaluronate. Viscoelastics were separated by a Debiopass™ stopper within a prefilled 3-ml sterile syringe. Injection was conducted for the LMW and HMW preparations as described above. Patients were free to seek additional therapeutic modalities including physical therapy and analgesics (including nonsteroidal anti-inflammatory drugs (NSAIDs)) but not intra-articular therapies prior to their presentation for follow-up. All concomitant treatments were recorded.

All injections were provided free of charge while neither participants nor the study was subsidized by any manufacturer.

Statistical analysis

Analysis of variance with repeated measures and X^2 test were used to test for differences from baseline characteristics of the group among the primary and secondary outcomes at each injection series interval. Analyses were conducted using sigma stat (SPSS Inc., Chicago, IL, USA) and Microsoft Excel (Microsoft Corp, Redmond, WA, USA). Significance was established at $p<0.05$ and included 95% Confidence Intervals (CI).

Results

Subject characteristics

Recruitment of participants was conducted over 6 months from referrals for assessment of osteoarthritis of the knee. The study population did not differ in baseline characteristics from the total referral group over the recruitment period. Subject disposition is shown in Fig. 2. Reasons for non-participation in the study included referral from a distant center, request for an alternate HA product and refusal to provide consent for intra-articular therapy. Study population and total referral baseline demographics are given in Table 1. There were no statistical differences between the study and referral populations at baseline. Most patients (79%) presented with unilateral knee osteoarthritis. In patients with bilateral symptoms, only the more symptomatic knee (on VAS) was used for the purposes of the study. The mean duration of symptoms was 7.4±4.1 years. Baseline mean seated resting VAS was 54.7±11.6 mm, 95% CI (41.4–58.5) and walking VAS was 76.7±9.4 mm, 95% CI (72.1–82.2).

Severity of knee osteoarthritis at baseline radiograph was graded as follows: 148 grade 1, 41 grade 2, and 11 grade 3. Overall concomitant medications use at baseline for osteoarthritis included acetaminophen (62%), NSAID–cyclooxygenase-2 (60%), and nutraceuticals (38%). Thirteen percent used physical therapy and/or bracing.

Ten subjects (placebo=3; DMW=2; LMW=1; HMW=4) dropped out for non-study-related reasons. There were no serious adverse events. Non-serious adverse events included pain and local swelling at the injection site (21%), erythema at the injection site (12%), and stiffness in the index knee (7%). There was no difference between groups for any of these reported events. None of the adverse events resulted in delay in study procedures.

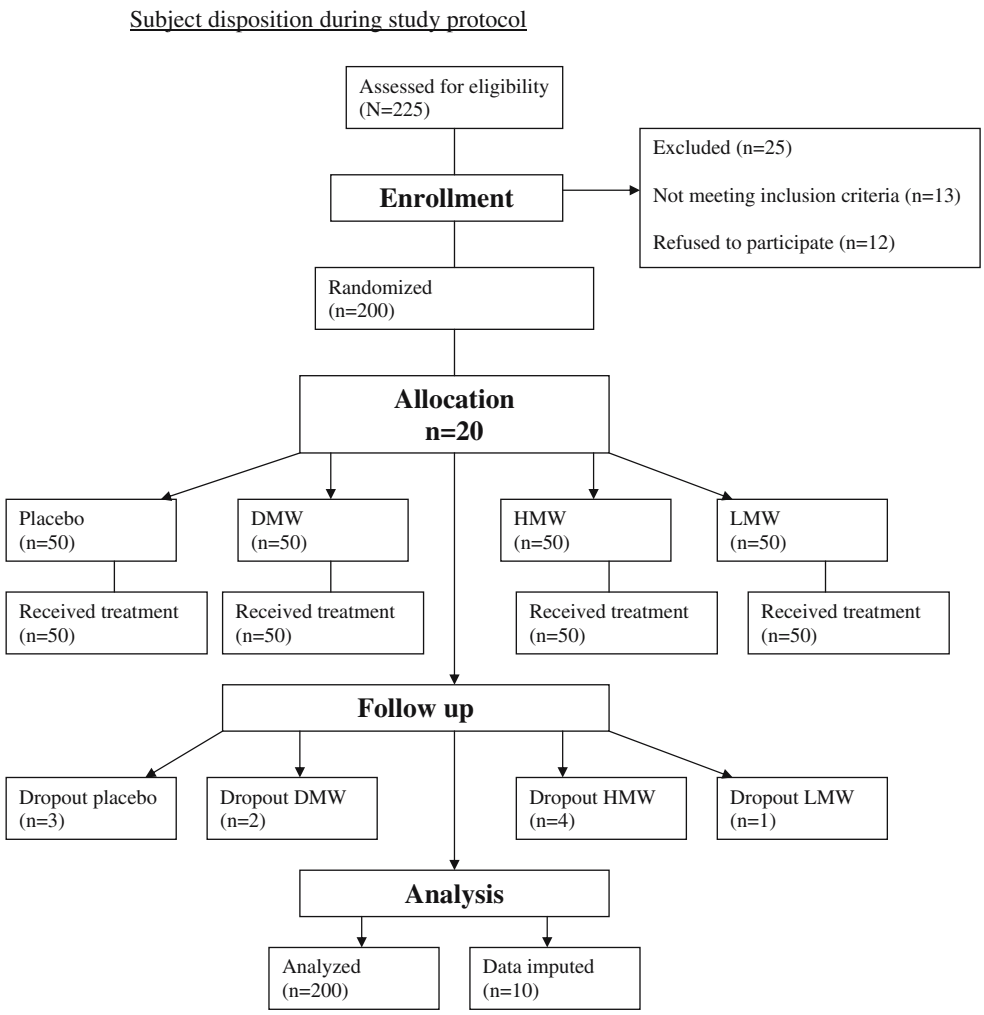

Fig. 2 Subject disposition during study protocol

Table 1 Baseline characteristics of experimental group and all other referrals during 3-month recruitment period

Variable	Placebo, *N*=50	DMW, *N*=50	LMW, *N*=50	HMW, *N*=50
Age (years)	71±8	68±6	69±5	71±9
Gender (female; *n*)	30	28	27	29
BMI (kg/m^2)	27.2±2.1	26.9±3.0	27.3±2.1	26.7±2.6
Years of OA symptoms	7.4±4.1	6.9±5.0	8.1±6.0	9.1±6.7
Grade knee OA (1 or 2; *n*)	39	41	41	38
Use of concomitant OA therapies (*n*)	3±1	2±1	3±2	2±1
Prior use of HA product (*n*)	10	7	9	7

Values mean±SD

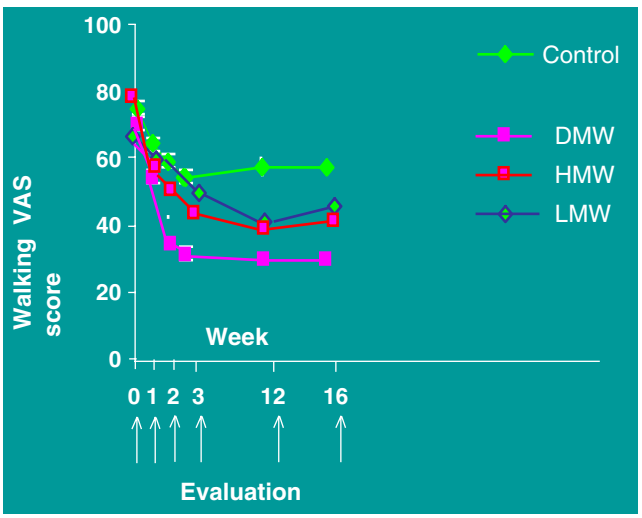

Fig. 3 Changes in walking VAS at 4, 12 and 16 weeks

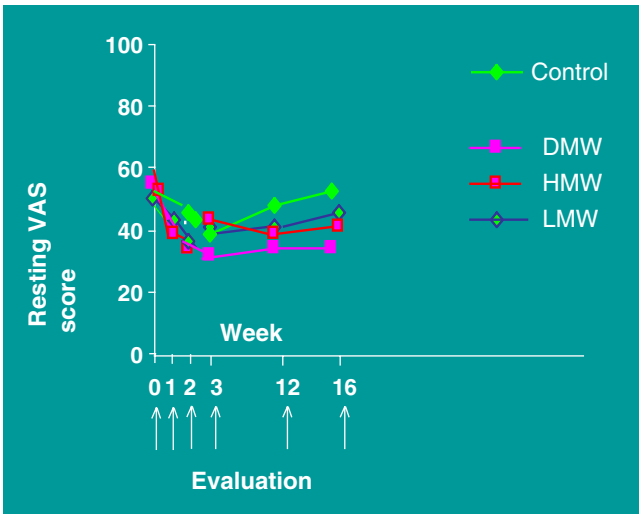

Fig. 4 Changes in rest VAS at 4, 12 and 16 weeks

Follow-up

At 4, 12, and 16 weeks, respectively, the change in walking VAS pain was significantly improved from baseline in all three active treatment groups: LMW (73.6%, $p<0.001$; 81.3%, $p<0.001$); HMW (69.1%, $p<0.001$; 78.1%, $p<0.001$), and DMW (79.6%, $p<0.001$; 89.3%, $p<0.001$; Fig. 3). There was no significant change in the placebo group at any time point. Patients in the DMW group had significantly greater improvement at 4, 12, and 16 weeks ($p<0.007$) compared to the other active treatment groups which did not differ from each other. Furthermore, the improvement in walking VAS pain was significantly greater from baseline and compared to other treatments at V3 (after the second injection) for DMW with no further changes following the third injection at 12 or 16 weeks follow-up (Fig. 3). Similarly, rest VAS pain was significantly decreased in all three active treatment groups from baseline at 4, 12, and 16 weeks; however, there was no significant difference among groups (Fig. 4). Use of concomitant therapeutic modalities at 4 weeks was not different among the active treatment groups and was low. In contrast, the placebo group significantly increased ($p<0.001$) the use of analgesics (i.e., Tylenol) at 4, 12, and 16 weeks while, significantly more LMW patients used concomitant therapeutic modalities at 16 weeks compared to the other two groups ($p<0.05$). Global satisfaction was significantly higher for the DMW group compared to the other groups at 16 weeks ($p<0.005$; Fig. 5). There was no difference between those with unilateral vs. bilateral knee OA.

Discussion

This study observed a significant improvement in pain at rest and with activity among patients with osteoarthritis of the knee randomized to one of LMW, HMW, or combined (DMW) HA interventions. However, we also observed that patients administered the DMW HA showed significantly lower activity-related pain, with fewer adverse events (low overall for all three treatments) and fewer concomitant therapeutic modalities after 16 weeks compared to either LMW or HMW-only treatments. DMW patients achieved maximum improvement in VAS pain following the second injection which was greater than the other treatments at any time point. Furthermore, patients in the DMW group showed significantly greater scores of satisfaction with their treatment at 12 and 16 weeks compared to the other two groups. These findings suggest combination of HA of lower and higher ranges of MW may provide patients with a more physiologically dynamic HA viscosupplementation and hence a more responsive synovial rheology that improves pain and function in their osteoarthritic knee. DMW is in a dual chamber syringe containing HA of both high and low molecular weights at low and high concentrations. HA of varying molecular weights have been

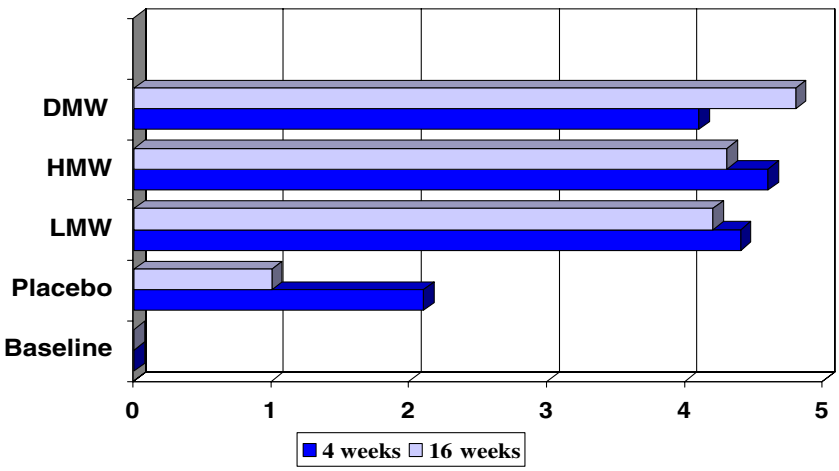

Fig. 5 Patient global satisfaction at 4 and 16 weeks

compared and yet there has been no conclusive evidence to support the superiority of any of them. HA concentration may play a more definite role and some published evidences suggest a direct effect over the viscosity of the synovial fluid as well as helping boundary lubrication and thin-film lubrication, both mechanisms which are implicated in the joint [20]. DMW contributes to the synovial fluids by increasing its elastic deformation when under load and hydrodynamic effect which forces contacting surfaces apart when the pressure of the load is deforming them [21]. This attributes to a higher capability of the synovial fluid in the protection of the joint and in weight bearing and moving [20].

Previous reports have described the efficacy of HA in patients with osteoarthritis of the knee [6–9]. Our findings in all three groups support HA as effective in improving symptoms and function in osteoarthritis of the knee with few adverse events. However, we were also interested in testing the hypothesis that synovial fluid, being a dynamic component of knee adaptation to loading of both high and low frequency, may, when compromised by the presence of osteoarthritis, require tailored viscosupplementation of HA that covers both the low and high ranges of MW needs. This concept is not new. Balasz and Denlinger [2] described a trend toward a progressive loss of a balance between elastic and viscous synovial fluid composition with presence (and progression) of osteoarthritis of the knee while Greenberg et al. [16] have more recently described the biochemical benefits of two different HAs in a co-culture model of OA. Hence, symptoms of pain with activity, of differing degree in different patients that changes in severity in time, may be related to this alteration of synovial fluid rheology. Viscosupplementation with HA is a therapeutic attempt to provide temporary relief of osteoarthritis symptoms based on these analogies. However, available products vary in the ranges of MW they contain—primarily being in lower or higher MW [14]. Hence, it seems reasonable to postulate that current viscosupplementation may fall short in providing patients with the mellieux of HA MW range they need to control their symptoms.

The key findings in our study was the significant improvement in pain and function with less use of concomitant therapies among patients randomized to DMW HA compared to either LMW or HMW alone. Furthermore, improvement was achieved with only two injections of DMW suggesting the benefit of combining two MWs may provide effects sooner and to a greater degree than with a HMW or LMW products alone. Limitations include the absence of longer-term data in terms of patient efficacy as well as comparison of multiple combinations of MW ranges and concentration of HA.

These limitations await further investigation. We utilized widely available HA products with standard dosing and injection regimen. However, it is possible that alternate dosing regimens, perhaps utilizing alternate molecular weight and concentration of HA could further impact these findings (including longer duration of effects) and require future investigation.

Hyaluronic acid injections were highly satisfactory to patients with each HA series and included a very low rate of local adverse events. This supports previous reports that HA treatment of osteoarthritis of the knee is a safe, effective therapeutic option. Our findings suggest that alteration of MW range may further improve outcomes in these patients.

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References

1. Dieppe P (1998) Osteoarthritis. Acta Orthop Scand 69(Suppl 281):2–5
2. Balasz EA, Denlinger SL (1993) Viscosupplementation: a new concept in the treatment of osteoarthritis. J Rheumatol 20(Suppl 39):3–9
3. Altman R, Moskowitz R, Felson DT, Anderson JJ (2002) Hyaluronate sodium injections for osteoarthritis: the truth. Arch Intern Med 162:2498–2500
4. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines (2000) Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 43(9):1905–1915
5. Dahlberg L, Lohmander LS, Ryd L (1994) Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain. Arthritis Rheum 37:521–528
6. Dougados M, Nguyen M, Listrat V, Amor B (1993) High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1-year placebo-controlled trial. Osteoarthr Cartil 1:97–103
7. Petrella RJ, DiSilvestro MD, Hildebrand C (2002) Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee. Arch Intern Med 162:292–298
8. Karlsson J, Sjogren LS, Lohmander LS (2002) Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis: a controlled, randomized, double-blind, parallel-design multicenter study. Rheumatology (Oxford) 41:1240–1248
9. Arrol B, Goodyear-Smith F (2004) Corticosteroid injections for osteoarthritis of the knee: meta-analysis. BMJ 328:869 Epub
10. Leopold SS, Redd BB, Warme WJ, Wehrle PA, Pettis PD, Shott S (2003) Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee: a prospective, randomized trial. J Bone Joint Surg 85:1197–1203
11. Adams ME, Atkinson MH, Lussier AJ et al (1995) The role of viscosupplementation with hylan GF-20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multi-centre trial comparing hylan GF-20 alone, hylan GF-20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthr Cartil 3:213–226
12. Lo GH, LaValley M, McAlindon T, Felson DT (2003) Intraarticular hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis. JAMA 290:3115–3121
13. Mamlin LA, Melfi CA, Parchman ML et al (1998) Management of osteoarthritis of the knee by primary care physicians. Arch Fam Med 7:563–567

14. Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B (2006) A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int 26:325–330
15. Kirchener M, Marshall D (2006) A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. Osteoarthr Cartil 14:154–162
16. Greenberg DD, Stoker A, Kane S, Cockrell M, Cook JL (2006) Biochemical effects of two different hyaluronic acid products in a co-culture model of osteoarthritis. Osteoarthr Cartil 14:814–822
17. Altman RD, Fries JF, Block DA et al (1987) Radiographic assessment of progression in osteoarthritis. Arthritis Rheum 30:1214–1225
18. Bellamy N (1997) Osteoarthritis clinical trials: candidate variables and clinimetric properties. J Rheumatol 24:768–778
19. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I (1996) Improving the quality of reporting clinical trials: the CONSORT statement. JAMA 276:637–639
20. Murakami T, Salai N, Sawae Y, Tanaka K, Ihara M (2004) Influence of proteoglycan on time-dependent mechanical behaviors of articular cartilage under constant total compressive deformation. JSME Int J 47:1049–1055
21. Ghosh P, Guidolin D (2002) Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: are the effects of molecular weight dependent? Semin Arthritis Rheum 32:10–37