Hyaluronic acid in the management of osteoarthritis: injection therapies innovations

Valter Santilli[1]
Marco Paoloni[1]
Massimiliano Mangone[2]
Federica Alviti[1]
Andrea Bernetti[1]

[1] Department of Physical Medicine and Rehabilitation, "Sapienza" University of Rome, Rome, Italy
[2] Fondazione "Don Carlo Gnocchi" Onlus

Address for correspondence:
Andrea Bernetti
Department of Physical Medicine and Rehabilitation
"Sapienza" University of Rome
Rome, Italy
E-mail: andrea.bernetti@uniroma1.it

Summary

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by pain and progressive functional limitation. Viscosupplementation with intra-articular (IA) hyaluronic acid (HA) could be a treatment option in OA, however recommendations made in different international guidelines for the non-surgical management of OA are not always concordant with regard to the role of IA injection therapies. Results from a recent Italian Consensus Conference underline how IA-HA to treat OA represents a widely used therapy in Italy. Specifically high molecular weight HA, cross-linked HA, and mobile reticulum HA are considered very useful to treat the OA joints from a great number of expert in Italy. These kinds of HA could reduce the NSAIDs intake, furthermore high-molecular weight and mobile reticulum HA are considered to be able to delay or avoid a joint prosthetic implant. This mini review highlights the results obtained from the Italian Consensus Conference "Appropriateness of clinical and organizational criteria for intra-articular injection therapies in osteoarthritis" and give further indication about innovation in IA-HA therapies.

KEY WORDS: hyaluronic acid; osteoarthritis; injections.

Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by progressive damage of articular cartilage and underlying bone. It is among the most common causes of pain and disability in European countries (1). Its estimated prevalence is 35% among people aged 50-59 years, and 55% for people over 70 years of age (2), while the lifetime risk for knee and hip OA is 45 (3) and 25% (4), respectively. The most important symptom of OA is pain, accompanied by morning stiffness, usually of short duration, that increases during movements and reduces with rest. Moreover, joint damage causes a progressive functional limitation (5). Intra-articular (IA) injections represent a therapy that is often used in the management of OA to deliver the therapeutic agent directly into the joint space. IA injection therapies seems to have a good safety profile and several products can be used (6), including steroids (7-10), hyaluronic acid (HA) (11, 12), platelet-rich plasma (PRP) (13) and polymerized collagen (14). Viscosupplementation (VS) with IA-HA represents a well-established treatment option especially in knee OA and it is included in the medical guidelines for treatment of the disease in this joint, but it could be applied, theoretically, to all synovial joints in order to reduce pain, improve joint function and delay joint damage. Interestingly, recommendations made in different international guidelines for the non-surgical management of OA are not always concordant with regard to the use of IA injection therapies (15). It should be borne in mind, however, that the results and recommendations made by the various organs are often biased by significant conflicts of interest, as showed by Printz et al. (16). Moreover, the therapeutic products used for OA are generally considered as a class, rather than as single products. For example, none of the guidelines makes any clear distinction between all the different formulations of HA, thereby possibly reducing the perceived impact of these products on the management of OA. Lastly, information on the optimal setting for IA injections is rarely provided in the recent guidelines for the management of OA. For all these reasons, it is crucial that the clinical issues and management of IA injections used to treat OA be defined on the basis of experiences shared by clinicians who have a high level of expertise in the use of these injections.

Results from "Appropriateness of clinical and organizational criteria for intra-articular injection therapies in osteoarthritis" a Delphi method consensus conference

From these points of view the Department of Physical Medicine and Rehabilitation of "Sapienza" University of Rome has developed a Delphi method Consensus Conference, on Appropriateness of clinical and organizational criteria for intra-articular injection therapies in osteoarthritis (17). A committee of 10 experts from Italian universities, public hospitals, territorial services, research institutes and patient associations was set up. The Consensus Board reviewed the literature and, on the basis of the drugs/medical devices currently available for IA injection therapies, developed the consensus' questionnaires. By analysing data from the questionnaires, the Board identified those statements that attained a wide consensus (more than 66%), which led to the definition of the recommendations. Analysing the Consensus results, IA injections are useful for mild to moderate OA of the hip, knee, ankle and shoulder. On the other side, the panel of experts agreed that IA injections are not useful to treat cervical and lumbar spine with OA. A consensus was not reached, both for agreement nor for disagreement as regards other sites, usually treated with IA injection therapies, like trapezium-metacarpal joint (17). The experts found

that IA injections are suitable for grade II/III OA as diagnosed accordingly to the Kellgren and Lawrence classification (17,18).
Furthermore, to select the most appropriate therapeutic product for IA injection therapy, the main variables taken into account by the experts were the safety profile, the rapid symptom relief, the long-term effect, the interaction with other therapies and also the scientific evidence of efficacy. Moreover, the choice of the product to be injected was also found to be influenced by the location of the OA process. In hip OA, experts believe that high-molecular weight HA (the distinction between high-, medium- and low-molecular weight HA was based on the product manufacturers' indications) and mobile reticulum (a partially hydrophobized derivative of HA stabilized by side-chain hydrophobic interactions) (19) HA are considered to be the most appropriate products. It is interesting to notice how there is no consensus on therapies that are widely used in everyday clinical practice, such as IA injection therapy with corticosteroids, polymerized collagen and PRP (17). Consequently, no recommendations could be made regarding their use. Consensus recommendations were not found on the possible exclusion criteria for IA injection therapy. It may be speculated, therefore, that the decision to exclude or not to exclude a patient from IA injection therapies needs to be evaluated on an individual basis. This hypothesis is confirmed by the agreement expressed by the experts regarding the low likelihood of minor or major side effects following IA injections, this is in line with the good safety profile reported for these treatment modalities. In particular, both corticosteroids and HA-IA injections are considered to relieve patients' symptoms. From these point of views, high-molecular weight, mobile reticulum and cross-linked HAs are, according to the interviewed experts, the products that most effectively reduce the systemic use of analgesic or NSAIDs, moreover IA injections with HA are considered to be valid as a means of controlling the objective manifestations of OA (17). This finding is supported by the experts' opinion about high-molecular weight and mobile reticulum HA, which are considered to be capable to delay or avoid a joint prosthetic implant (20). Considering radiologic or ultrasound guidance for IA injections, it is assumed to be necessary for hip IA injections, but not for knee IA injections. In addiction to these considerations, there is not a widespread consensus in the literature regarding the need for radiologic or ultrasound guidance when performing IA injections. However, as opposed to unguided procedures, guided IA injections are reported to be more accurate and safer. Indeed, guided IA injections could permit a better clinical outcome in terms of joint function improvement and in a decreased risk of damage due to procedure accuracy. Moreover, it should be borne in mind that imaging techniques used for IA injection are obviously extremely important in the global management of OA patients, particularly if a differential diagnosis is needed (17).

Hyaluronic acid: injection therapies innovations

Osteoarthritis (OA) is characterized by joint pain and stiffness with accompanying disability and loss of quality of life. All joint tissues, including capsule, synovium, intra-articular ligaments and menisci, bone and cartilage are involved in OA. The articular cartilage within affected joints is degraded and lost, thus ceasing to function as a frictionless bearing surface. While it is the ultimate loss of cartilage that often necessitates the need for joint replacement, subchondral bone lesions and synovial/joint capsule inflammation and fibrosis appear to be the major causes of OA pain. Current treatments for OA are often limited and are either pain-relieving or involve joint replacement at end-stage disease. Actually the challenge is to find treatments that could exhibit potential of structural modifications to restore function. HA is a non-sulfated glycosaminoglycan consisting of alternately repeating D-glucuronic acid and N-acetylglucosamine units. HA exists naturally in various animal tissues, the highest amounts of HA in the human body are found in the extracellular matrix of soft connective tissues (21). HA could bind to specific receptors expressed in many cells, such as the cluster determinant 44 (CD44), the intracellular adhesion molecule-1 (ICAM-1) and the receptor for hyaluronate-mediated motility (RHAMM) (22, 23). The consequences of these connections is to stimulate cell functional activities such as cell migration and proliferation (24). In osteoarthritic joints synovial fluid always contains a lower concentration of HA than in healthy joints, so IA injections therapy with exogenous kind of HA can restore its viscoelastic properties. Globally, data indicate that IA-HA provide OA pain relief that is comparable to or greater than that observed with conventional treatment, NSAID medications, intra-articular corticosteroids, arthroscopic lavage, physical therapy and exercise (25). In patients with OA NSAIDs consumption, in order to reduce pain, is often inappropriate and strongly related to both high gastrointestinal and cardiovascular morbidity and increasing mortality rate. Instead, HA-IA treatment is well tolerated and is associated with a low incidence of adverse effects (26). Recent meta-analyses have concluded that IA-HA treatment for OA should be considered as a longer-term therapy than other treatments, with a clinically relevant effect size equivalent or greater than other analgesics (27, 28). Furthermore, treatment with repeated cycles of IA-HA seems to delay surgical interventions in knee and hip osteoarthritis as shown by several studies (29-31). Despite this evidence, the mechanism(s) by which HA alleviates joint pain remains not clear. *In vivo* and *in vitro* studies have shown various physiological effects of exogenous HA that should contrast the mechanisms involved in OA pathogenesis. Indeed, exogenous HA can enhance chondrocyte synthesis of endogenous HA and proteoglycans prevent the degradation of cartilage and promote its regeneration. Moreover, HA can reduce the production of proinflammatory mediators and matrix metalloproteinases, and could reduce nerve impulses and nerve sensitivity associated with OA pain. In fact, IA-HA therapy can lead to modulation of nociceptors (32), reduction of synovial/capsular fibrosis (33), increased synthesis of higher molecular weight endogenous HA by the resident synoviocytes (33, 34), and reduction in inflammatory mediators including prostaglandin-E2, IL-1 and IL-6 (35-37). Furthermore, there is significant evidence that IA-HA injections could reduce the rate of cartilage degeneration in animal models of OA (38-40) but whether the same could happen in humans is unclear. Amelioration of cartilage degradation by HA is thought to occur through enhancement of chondrocyte aggrecan synthesis (41, 42), reduction of matrix degrading enzyme [matrix metalloproteinases (MMPs) (43) and disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) (44)], and modification of inflammatory cytokine expression and activity (32). The latter could also being implicated in symptom modification. From these points of view it is interestingly to note how a hexadecylamide derivative of HA (mobile reticulum HA) has superior beneficial effects on human osteoarthritic chondrocytes and synoviocytes than unmodified hyaluronan (45). In fact the more recent types of HA are formulated to act not only on the synovial fluid constitution or on joints physical characteristics, but also on joints biologic structure, especially on its cartilaginous surface. Moreover, a recent research (45) showed how hexadecylamide derivative of HA (mobile reticulum HA) could ameliorate IL-1-induced expression and/or activity of key matrix degrading enzymes (*MMP1, MMP13, ADAMTS5*), and inflammatory mediators (*IL6*, *PTGS2*) by chondrocytes and synovial fibroblasts. This is associated in part with a greater inhibition of cell signalling molecule (JNK, p38 and NFκB) phosphorylation in chondrocytes, to-

gether suggesting mechanisms whereby the hexadecylamide derivative of HA (mobile reticulum HA) may be beneficial. Furthermore these kind of HA could also ideally be used as a hydrogel seeded with bone marrow-derived mesenchymal stem cells (BMSCs), as a method of regenerating these tissues for OA therapy. The delivery of autologous chondrocytes (46) or mesenchymal stem cells (MSCs) (47) for cartilage regeneration has shown some promising results. MSCs in particular have received much attention for their potential role in cartilage regeneration, as they are multipotent cells capable of differentiating into cartilage, bone, muscle, fat and marrow stroma in response to appropriate signalling pathways. HA scaffolds have been well established as a biomaterial (48) for MSC delivery. HA hydrogels have been used to induce MSC osteogenesis, adipogenesis and keratinogenesis (48) *in vitro.* Chung et al. reported that delivery of MSCs in HA hydrogels promoted chondrogenic gene expression (49). Finally HA is known to directly interact with the fibrin precursor fibrinogen through reversible complex ionic interactions (50).
In addition to these considerations about IA-HA injection therapies for OA, HA is recently been used as peri-tendineous injection to treat tendinopathies as the epicondylitis (51), the patellar tendinopathy and the insertional Achilles tendinopathy (52).
Finally, the more recent treatments for osteoarthritic joints, and other musculoskeletal conditions, should be studied not only with conventional radiology but also from a biomechanical point of view in order to understand joint's kinematic and kinetic thee dimensional alterations due to the pathological process. This kind of studies could be conducted in a laboratory of movement analysis (53), or using a wearable inertial sensor in order to assess joint mobility and muscle strength (54).

Conclusion

HA is an useful tool in the management of patients with osteoarthritis, literature data seem to indicate its ability to reduce pain and improve joint function, with a potential structure modifying activity. Results from a recent Consensus Conference, on Appropriateness of clinical and organizational criteria for intra-articular injection therapies in osteoarthritis (17), showed how in hip OA, experts believe that high-molecular weight HA and mobile reticulum (19) HA are considered to be the most appropriate products. Furthermore, IA injections using high molecular weight HA, cross-linked HA, and mobile reticulum HA are also considered very effective from a great number of expert in Italy, to treat OA. In fact, these kind of HA could reduce the NSAIDs intake, furthermore high-molecular weight and mobile reticulum HA are considered to be able to delay or avoid a joint prosthetic implant. Furthermore hexadecylamide derivative of HA (mobile reticulum HA) has superior beneficial effects on human osteoarthritic chondrocytes and synoviocytes than unmodified hyaluronan. Imaging techniques used for IA injection guidance may be extremely important in the management of patients with OA, specifically the radiologic guidance represent a fundamental help in order to perform hip joint injections (17). Further research are needed to evaluate the long-term clinical effect of IA injection with MSC using HA as scaffold. Moreover, HA peri-tendineous injections could be used with success to treat tendinopathies as the epicondylitis (51), the patellar tendinopathy and the insertional Achilles tendinopathy (52). In conclusion, considering its clinical and structural effectiveness and its tolerability, therapy with HA can be considered as a long-term therapy.

References

1. Kingsbury SR, Gross HJ, Isherwood G, Conaghan PG. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. Rheumatology (Oxford). 2014;53(5):93747.
2. Hunter DJ, Neogi T, Hochberg MC. Quality of osteoarthritis management and the need for reform in the US. Arthritis Care Res (Hoboken). 2011;63(1):31-8.
3. Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, Dragomir A, Kalsbeek WD, Luta G, Jordan JM. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum. 2008;59(9):1207-13.
4. Murphy LB, Helmick CG, Schwartz TA, Renner JB, Tudor G, Koch GG, Dragomir AD, Kalsbeek WD, Luta G, Jordan JM. One in four people may develop symptomatic hip osteoarthritis in his or her lifetime. Osteoarthritis Cartilage. 2010;18(11):1372-9.
5. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet. 2011;377:2115-26.
6. Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. World J Orthop. 2014;5(3):351-61.
7. Jones A, Doherty M. Intra-articular corticosteroids are effective in osteoarthritis but there are no clinical predictors of response. Ann Rheum Dis. 1996;55(11):829-32.
8. Robinson P, Keenan AM, Conaghan PG. Clinical effectiveness and dose response of image-guided intra-articular corticosteroid injection for hip osteoarthritis. Rheumatology (Oxford). 2007;46(2):285-91.
9. Di Sante, L, Paoloni M, Dimaggio M, Colella L, Cerino A, Bernetti A, Murgia M, Santilli V. Ultrasound-guided aspiration and corticosteroid injection compared to horizontal therapy for treatment of knee osteoarthritis complicated with Baker's cyst: a randomized, controlled trial. Eur J Phys Rehabil Med. 2012;48(4):561-7.
10. Yavuz U, Sökücü S, Albayrak A, Oztürk K. Efficacy comparisons of the intraarticular steroidal agents in the patients with knee osteoarthritis. Rheumatol Int. 2012;32(11):3391-6.
11. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum. 2014;43(5):593-9.
12. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. BioDrugs. 2012;26(4):257-68.
13. Pourcho AM, Smith J, Wisniewski SJ, Sellon JL. Intraarticular platelet-rich plasma injection in the treatment of knee osteoarthritis: review and recommendations. Am J Phys Med Rehabil. 2014;93(11 Suppl 3): S108-21.
14. Furuzawa-Carballeda J, Lima G, Llorente L, NuñezÁlvarez C, Ruiz-Ordaz BH, Echevarría-Zuno S, Hernández-Cuevas VL. Polymerized-type I collagen downregulates inflammation and improves clinical outcomes in patients with symptomatic knee osteoarthritis following arthroscopic lavage: a randomized, double-blind, and placebo-controlled clinical trial. Scientific World Journal. 2012;2012:342854.
15. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum. 2014;43(6):701-12.
16. Printz JO, Lee JJ, Knesek M, Urquhart AG. Conflict of interest in the assessment of hyaluronic acid injections for osteoarthritis of the knee: an updated systematic review. J Arthroplasty. 2013 Sep;28(8 Suppl):30-33.e1. doi:10.1016/j.arth.2013.05.034. Epub 2013 Jul 24. Review.
17. Paoloni M, Bernetti A, Belelli A, Brignoli O, Buoso S, Caputi AP, Catani F, Coclite D, Fini M, Mantovani L, Migliore A, Napoletano A, Viora U, Santilli V. Appropriateness of clinical and organizational criteria for intra-articular injection therapies in osteoarthritis. A Delphi method consensus initiative among experts in Italy. Ann Ist Super Sanità. 2015; 51(2):131-8.

18. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis. 1957;16(4):494-502.
19. Finelli I, et al. A new viscosupplement based on partially hydrophobic hyaluronic. Biorheology. 2011;48(5):263-75.
20. Romero Jurado M, et al. Factors related with the time to surgery in waiting-list patients for knee prostheses. Reumatol Clin. 2013;9(3):148-55.
21. Iannitti T, Lodi D, Palmieri B. Intra-articular injections for the treatment of osteoarthritis: focus on the clinical use of hyaluronic acid. Drugs R D. 2011;11(1):13-27. Review.
22. Hodge-Dufour J, Noble PW, Horton MR, et al. Induction of IL-12 and chemokines by hyaluronan requires adhesion-dependent priming of resident but not elicited macrophages. J Immunol. 1997;159:2492-500.
23. Siegelman MH, DeGrendele HC, Estess P. Activation and interaction of CD44 and hyaluronan in immunological system. J Leukoc Biol. 1999;66:315-21.
24. Cao JJ, Singleton PA, Majumdar S, et al. Hyaluronan increases RANKL expression in bone marrow stromal cells through CD44. J Bone Miner Res. 2005;20:30-40.
25. Waddell DD. Viscosupplementation with hyaluronans for osteoarthritis of the knee: clinical efficacy and economic implications. Drugs Aging. 2007;24(8):629-42. Review.
26. Migliore A, Procopio S. Effectiveness and utility of hyaluronic acid in osteoarthritis. Clin Cases Miner Bone Metab. 2015 Jan-Apr;12(1):31-3. doi: 10.11138/ccmbm/2015.12.1.031. Review. PubMed PMID: 26136793.
27. Bannuru RR, Natov NS, Dasi UR, Schmid CH, Mcalindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis - meta-analysis. Osteoarthritis Cartilage. 2011;19:611-619. doi: 10.1016/j.joca.2010.09.014.
28. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006. p. CD005321.
29. Turajane T, Amphansap T, Labpiboonpong V, et al. Total knee replacement following repeated cycles of intra-articular sodium hyaluronate (500-730 Kda) in failed conservative treatment of knee osteoarthritis: a 54-month follow-up. J Med Assoc Thai. 2009 Dec;92 Suppl 6:S63-8.
30. Waddell DD, Bricker DC. Total knee replacement delayed with Hylan GF 20 use in patients with grade IV osteoarthritis. J Manag Care Pharm. 2007 Mar;13(2):113-121.
31. Van den Bekerom MP, Rys B, Mulier M. Viscosupplementation in the hip: evaluation of hyaluronic acid formulations. Arch Orthop Trauma Surg. 2008 Mar;128(3):275-80. Epub 2007 Jun 16.
32. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis Res Ther. 2003;5:54-67.
33. Smith MM, Cake MA, Ghosh P, Schiavinato A, Read RA, Little CB. Significant synovial pathology in a meniscectomy model of osteoarthritis: modification by intra-articular hyaluronan therapy. Rheumatol. 2008;47:1172-1178. doi: 10.1093/rheumatology/ken219.
34. Smith MM, Ghosh P. The synthesis of hyaluronic acid by human synovial fibroblasts is influenced by the nature of the hyaluronate in the extracellular environment. Rheumatol Int. 1987;7:113-122. doi: 10.1007/BF00270463.
35. Hashizume M, Mihara M. High molecular weight hyaluronic acid inhibits IL-6-induced MMP production from human chondrocytes by up-regulating the ERK inhibitor, MKP-1. Biochem Biophys Res Commun. 2010;403:184-189. doi: 10.1016/j.bbrc.2010.10.135.
36. Takahashi K, Goomer RS, Harwood F, Kubo T, Hirasawa Y, Amiel D. The effects of hyaluronan on matrix metalloproteinase-3 (MMP-3), interleukin-1beta(IL-1beta), and tissue inhibitor of metalloproteinase-1 (TIMP-1) gene expression during the development of osteoarthritis. Osteoarthritis Cartilage. 1999;7:182-190. doi: 10.1053/joca.1998.0207.
37. Yasuda T. Hyaluronan inhibits prostaglandin E2 production via CD44 in U937 human macrophages. Tohoku J Exp Med. 2010;220:229-235. doi: 10.1620/tjem.220.229.
38. Kim SS, Kang MS, Lee KY, Lee MJ, Wang L, Kim HJ. Therapeutic effects of mesenchymal stem cells and hyaluronic acid injection on osteochondral defects in rabbits' knees. Knee Surg Rel Res. 2012;24:164-172. doi: 10.5792/ksrr.2012.24.3.164.
39. Tsai W-Y, Wu J-L, Liu C-C, Cherng C-H, Tsai R-Y, Jean Y-H, Wong C-S. Early intraarticular injection of hyaluronic acid attenuates osteoarthritis progression in anterior cruciate ligament-transected rats. Connect Tissue Res. 2013;54:49-54. doi: 10.3109/03008207.2012.734877.
40. Goldberg V, Buckwalter JA. Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity. Osteoarthritis Cartilage. 2005;13:216-224. doi: 10.1016/j.joca.2004.11.010.
41. Frean S, Abraham L, Lees P. In vitro stimulation of equine articular cartilage proteoglycan synthesis by hyaluronan and carprofen. Res Vet Sci. 1999;67:183-190. doi: 10.1053/rvsc.1999.0328.
42. Fukuda K, Dan H, Takayama M, Kumano F, Saitoh M, Tanaka S. Hyaluronic acid increases proteoglycan synthesis in bovine articular cartilage in the presence of interleukin-1. J Pharmacol Exp Ther. 1996; 277:1672-1675.
43. Julovi S, Yasuda T, Shimizu M, Hiramitsu T, Nakamura T. Inhibition of interleukin-1β-stimulated production of matrix metalloproteinases by hyaluronan via CD44 in human articular cartilage. Arthritis Rheum. 2004;50:516-525. doi: 10.1002/art.20004.
44. Yatabe T, Mochizuki S, Takizawa M, Chijiiwa M, Okada A, Kimura T, Fujita Y, Matsumoto H, Toyama Y, Okada Y. Hyaluronan inhibits expression of ADAMTS4 (aggrecanase-1) in human osteoarthritic chondrocytes. Ann Rheum Dis. 2009;68:1051-1058. doi: 10.1136/ard.2007.086884
45. Smith MM, Russell AK, Schiavinato A, Little CB. A hexadecylamide derivative of hyaluronan (HYMOVIS®) has superior beneficial effects on human osteoarthritic chondrocytes and synoviocytes than unmodified hyaluronan. J Inflamm (Lond). 2013 Jul 27;10:26.
46. Vasiliadis HS, Danielson B, Ljungberg M, McKeon B, Lindahl A, Peterson L. Autologous chondrocyte implantation in cartilage lesions of the knee. Long-term evaluation with magnetic resonance imaging and delayed gadolinium-enhanced magnetic resonance imaging technique. Am J Sports Med. 2010;38:943-949.
47. Galle J, Bader A, Hepp P, Grill W, Fuchs B, Kas JA, Krinner A, Marquass B, Muller K, Schiller J, Schulz RM, von Buttlar M, von der Burg E, Zscharnack M, Loffler M. Mesenchymal stem cells in cartilage repair: State of the art and methods to monitor cell growth, differentiation and cartilage regeneration. Curr Med Chem. 2010;17(21):2274-91.
48. Bian L, Hou C, Tous E, Rai R, Mauck RL, Burdick JA. The influence of hyaluronic acid hydrogel crosslinking density and macromolecular diffusivity on human MSC chondrogenesis and hypertrophy. Biomaterials. 2013;34:413-421.
49. Chung C, Burdick JA. Influence of three-dimensional hyaluronic acid microenvironments on mesenchymal stem cell chondrogenesis. Tissue Eng Part A. 2009;15:243-254.
50. LeBoeuf RD, Raja RH, Fuller GM, Weigel PH. Human fibrinogen specifically binds hyaluronic acid. J Biol Chem. 1986;261:12586-12592.
51. Bernetti A, Mangone M, Paoloni M, Di Sante L, Murgia M, Santilli V. Corticosteroidi ed acido ialuronico per via infiltrativa nel trattamento del gomito del tennista (epicondilite laterale). Medicina dello Sport. 2014; 67(2):289-95.
52. Kumai T, Muneta T, Tsuchiya A, Shiraishi M, Ishizaki Y, Sugimoto K, Samoto N, Isomoto S, Tanaka Y, Takakura Y. The short-term effect after a single injection of high-molecular-weight hyaluronic acid in patients with enthesopathies (lateral epicondylitis, patellar tendinopathy, insertional Achilles tendinopathy, and plantar fasciitis): a preliminary study. J Orthop Sci. 2014;19(4):603-11.
53. Paoloni M, Di Sante L, Dimaggio M, Bernetti A, Mangone M, Di Renzo S, Santilli V. Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular injections of hyaluronic acid. Clin Biomech (Bristol, Avon). 2012 Aug;27(7):661-5.
54. Tranquilli C, Bernetti A, Picerno P. Ambulatory joint mobility and muscle strength assessment during rehabilitation using a single wearable inertial sensor. Medicina dello sport. 2013;66(4):583-97.