I.S.Mu.L.T. Hyaluronic acid injections in musculoskeletal disorders guidelines

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Summary

Intra-articular and peri-articular hyaluronic acid (HA) injections are widely used to treat several musculoskeletal pathologies. Although clinical

outcomes are often positive for different conditions, an holistic consensus on this topic is still lacking. Our work is divided in two main sessions: in the first section we analyzed the preclinical bases for HA treatment in musculoskeletal pathologies, while in the second part we discussed the evidence on the use of HA injections in each district of musculoskeletal system. The aim of this work is to provide to the physician a feasible guideline rapidly to consult in the clinical practice.
Level of evidence: Ia.

Approach to guidelines

These recommendations developed through a process of systematic review of the literature and expert opinion, to be used to improve the quality of care and rationalize the use of resources.
Clinical decisions on individual patients require the application of the recommendations, based on the best scientific evidence and clinical experience of the physician.

Methodology

The Authors were divided into four groups:
- a coordinator conceived and organized the work and the groups, and selected the most important questions on the topic at hand;
- a overseeing group controlled the development of the work and discussed the recommendations;
- the group of the experts individually received a question and developed the answers according to the rules of EBM, when it was possible;
- the group of preparation and evaluation of literature drew up the text and assisted the group of experts in evaluating the literature.

Methods and criteria of study selection

For the research were consulted the following databases:
- PubMed
- Embase
- Google Scholar
- Cochrane Library.

Randomized controlled trials (RCTs); systematic reviews; to follow if missing the first two, the other levels of evidence. The literature is updated at December, 2016.

Level of evidence

Level of evidence	*Criteria for analysis and inclusion*
I	Meta-analyses and systematic reviews of randomized controlled trials (RCTs) of high quality, or RCTs with minimum or low risk of bias. Systematic reviews of high quality relative to cohort studies or case-control.
II	Cohort studies or randomized case-control high quality, with minimal risk of confounding or bias and with high or discrete probability of causation.
III	Case-control studies and retrospective comparison of well-conducted with reasonable probability of causation.
IV	Non-analytic studies as case series or individual cases.

Level of recommendation

Level of recommendation	*Criteria for analysis*
A	Supported by at least two studies of level Ib or from a review level Ia ("it was shown").
B	Supported by at least two independent studies of level II or extrapolations from studies of level I ("it is possible").
C	Not supported by adequate studies of level I or II ("indications").
D	Indications of experts ("there is no evidence").

Hyaluronic acid

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan (GAG), formed by repetitive units of glucuronic acid and N-acetyl glucosamine, widely express in the extracellular matrix (ECM) to confer protection, shape and mechanical support to cells and tissues. HA for its composition and expression is a key-component of cartilage and tendon structures, where it contributes to viscoelastic properties[1-5]. Stiff segments, linked by flexible domains to confer a super-helix, form the 50-70% of the molecule[6]. Therefore, viscoelastic properties of HA solutions can therefore be explained by the development of a dynamic three-dimensional network formed by transient associations between stiff segments[7-9].
However, the importance of this molecule depends in part by its structure and hygroscopic properties, in part by the interaction with a large number of surface and intracellular receptors: CD44 glycoproteins, ICAM-1 and RHAMM, HARE, and intracellular proteins binding the hyaluronic acid CDC37, RHAMM/IHABP, P-32 and IHABP4[10-12].

Injection techniques and good clinical practice

Intra-articular and peri-articular procedures should be accomplished in adequate clinical settings following evidence based medical recommendations and a point-to-point procedure[13-15]:
- collect history and clinical examination;
- obtain oral/written informed consent;
- prepare the equipment;
- prepare the patient;
- disinfect the skin before and after the injection;
- program follow-up evaluation.

The equipment required is:
- gloves/sterile gloves;
- sterile swabs and sterile draps;
- prepacked sterile needles and syringes;

- disinfectant (iodopovidone/chlorexidhine);
- synovial fluid collection bottles;
- sterile ultrasound kit (only for US-guided injection);
- emergency kit[16,17].

The choice of the right needle is mandatory, considering the characteristics of the target joint. A needle of 21 gauge should be preferred in large joints as the shoulder or the knee, while 23-25 gouge needles are indicated in small joints[13]. Deep joints as the hip required the adoption of spinal needles (length of 3,5 inches; 8-9 centimeters)[18].

Clinicians should identify any possible contraindications to the procedure. Absolute contraindications are: systemic infections and bacteremia, articular infections, skin lesions in the area, osteomyelitis, septic arthritis, unstable coagulopathy and severe thrombocytopenia, allergy (hypersensitivity) to any of the components and pregnancy. Injections procedures should be carefully performed in patients that use anticoagulants or other medications that alter INR. Injections should be avoid in patients with prolonged bleeding time or platelet count < 100 000/µl[18].

Generally, adverse effects are local and well-tolerated. Common local side effects are redness and pain in the site of injection (<72 hours after injection). Septic arthritis is rare (1:1000), while some cases of calcium pyrophosphate dihydrate crystal deposition disease (CPPD) are documented to be exacerbated by hyaluronic acid injections. Cross-linked products were related to severe acute inflammatory reaction (SAIR), a pseudo-septic condition probably related to immune-response mechanisms[13,19,20].

Key points

- The injection should always be performed respecting sterile standardized procedures. It is mandatory to carefully disinfect the area preferring chlorhexidine preparations, mixtures of chlorhexidine gluconate and ethyl alcohol, iodopovidone solutions and analogs.
- The choice of the needle should consider the type of injection, the characteristics of the target joint and patient.
- Injection could be precede by arthrocentesis, which is helpful to the diagnosis of underlying pathological process in selected patients.
- Patients should observe a waiting period of 20-30 minutes in an outpatient facility after the injection.

KEY WORDS: musculoskeletal injection, guidelines, hyaluronic acid, principles, accuracy, disinfection.

Hyaluronic acid properties in joint disorders and osteoarthritis

It was demonstrated that HA should protect articular environment through several mechanisms of action: anti-inflammatory effect, chondroprotection, analgesic effect, subchondral bone protection and increased production of endogenous HA.

Anti-inflammatory effect

Several *in vitro* and *in vivo* studies suggest that anti-inflammatory action is determined by the reduction of the principal mediators of inflammation as IL-1[21], TNF-α[22], IL-6, IL-8[23] and prostaglandin E2 (PGE2)[24,25]. Interaction with CD44 leads to decrease in IL-1β and metalloproteinases (MMPs) in cartilage and synovial fluid[21,26], decrease in PGE2 expression in synovial fluid[27], increase of TIMP-1 production and inhibition of anti-inflammatory response[28].

New products as HYADD-4 (Hymovis®, Fidia Farmaceutici SpA, Abano Terme, Italy) and H/L-HA (Sinovial HL®, IBSA SA, Switzerland) may determine a better anti-inflammatory response[29,30].

Chondroprotection

Chondroprotection is determined by the reduction of chondrocyte apoptosis and by the increase in chondrocyte proliferation and viability, with the consequent increase in the production of ECM components (GAGs and PGs)[31-34]. Increased viability and proliferation is due in part to the down-regulation of proteolytic enzymes as MMPs and aggrecanases (ADAMTS)[35-38].

Anti-apoptotic effects is linked to different mechanisms as Fas/Fas-ligand and mithocondrial function[39-44].

Analgesic effect

HA seems to exert analgesic effects through different mechanisms. In part, this action should be explained by the modulation of nociception due to down-regulation of main inflammatory mediators, as PGE2 and bradykinin[45-49]. Furthermore, viscoelastic properties of HA should reduce mechanical forces transmitted to nociceptive endings[50-52]. Recent findings evidenced that HA can induce activation of k-opioid receptor (KOP), suggesting other possible pathways of analgesic activity[53].

Subchondral bone protection

HA can directly reduce osteoblast expression of MMP-13 and IL-1ß induced expression of MMP-3, ADAMTS-4 and ADAMTS-5[54,55]. HA should also act on osteoclasts enhancing expression of osteoprotegerin (OPG) and inhibiting RANK-ligand[56,57].

Production of endogenous HA

HA injections determine a concentration dependent increase of endogenous HA production[57]. Endogenous HA concentration was found to be increased also at 3 and 6 months post-injection[58-61].

Keypoints

- HA intra-articular injections could determine disease-modifying effects through several mechanisms of action: anti-inflammatory effect, chondroprotection, analgesic effect, subchondral bone protection and increased production of endogenous HA.
- Currently it is not clear whether any formulation is

superior as disease-modifying molecule.
- New formulations (HYADD-4, H/L-HA) may determine a greater anti-inflammatory effect.

Level of recommendation: A.

KEY WORDS: hyaluronic acid, chondroprotection, cartilage, subchondral bone, anti-inflammatory, intra-articular, osteoarthritis, chondrocyte, osteoblast.

Hyaluronic acid properties in soft tissues: tendons, ligaments and bursas

Tendons

HA should enhance tenocyte viability and proliferation and reduce collagen III production, while it is not well established if HA may determine increase in collagen I production[62-64].

Keypoints
- In Achilles tendinopathy, HA injections stimulate healing process, reducing adhesion formation and regulating the expression of vascular endothelial growth factor (VEGF) and type IV collagen[65].
- In rotator cuff diseases, HA injections exert mechanical (anti-adhesion) and biological effects (reduction of PGE2, C4S, IL-1 and modulation of leukocytes migration)[66].
- In patellar tendinopathy, HA injections associated to rest should increase anabolic metabolism of tenocytes [67,68].

Level of recommendation: B.

Ligaments

Actually, there are no evidences that support the use of HA injections in ligament pathologies or a direct action of HA on ligament structure. Some trials suggest the possible role of early HA injection after ACL surgery[69].

Level of recommendation: D.

Bursas

Some studies have recently investigated the possible role of US-guided injections importance in different bursas, including the subacromial bursa[70]; however, it is not univocally known whether HA could improve the composition of the synovial fluid of bursa pathologies[71].

Level of recommendation: D.

Hyaluronic acid in shoulder disorders

Shoulder pain is common in general population[72] and could be referred to rotator cuff tendinopathy, glenohumeral osteoarthritis or acromionclavear osteoarthritis[73,74]. Capsulitis should also be considered and it could be idiopathic or secondary to intraarticular and extra-articular pathologies. The use of NSAIDs is considered the first line treatment, but injection procedures should be indicated in non-responders patients.

Glenohumeral injections

Intra-articular injections in glenohumeral joint are widely used in clinical practice and several studies promote the efficacy in short and medium term[75-84] (Tab. I). Intra-articular injections in glenohumeral joint are proposed for different pathologies, as osteoarthritis and rotator cuff pathology and frozen shoulder.

Level of recommendation: A.

Adhesive capsulitis

Several Authors evaluated the role of HA injections in adhesive capsulitis, but in many studies patients affected by AC represent a subgroup[75,84,85-88]. Injection therapy should be considered in a multimodal approach that includes capsular stretching and exercise therapy.

Level of recommendation: B.

Subacromial injections

Five studies were selected (Tab. II)[89-93]. Subacromial injections are proposed in rotator cuff pathology or subacromial space syndrome. This procedure should be ultrasound-guided to permit sufficient accuracy.

Level of recommendation: A.

Key points
- Intra-articular injections in glenohumeral joint should determine a great efficacy in osteoarthritis in short and medium term, while the procedure is not superior to other therapies in ROM improvement in adhesive capsulitis.
- Ultrasound-guided subacromial injections improve pain and function in rotator cuff pathology.
- There is lack of evidence about the possible role of HA in acromion-clavicular disorders.

KEY WORDS: hyaluronic acid, tendon, tendinopathy, ligaments, extra-articular.

Hyaluronic acid in elbow disorders

Lateral epicondylitis

Lateral elbow pain could be reported in several pathologies as chondromatosis, chondral lesions, intra-articular loose bodies, elbow instability or posterior interosseus nerve syndrome.

Thus, correct differential diagnosis is mandatory to achieve good clinical outcomes.

Several conservative modalities were described to treat lateral tennis elbow syndrome, while surgery is indicated only in refractory cases.

Only one RCT and few level IV trials investigated the possible role of HA in epicondylitis (Tab. III)[68,94,95].

These studies are heterogeneous for methodologies neither use US-guidance.

Level of recommendation: B.

Elbow osteoarthritis

Elbow is not a common site of osteoarthritis, characterized by cartilage loss, osteophytes formation and intra-articular loose bodies.

The low prevalence should partially explain that the

Table I. Selected studies on intra-articular glenohumeral injections.

Author and year	Study design	Protocol/pathology	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Blaine et al. 2008[75]	RCT	5 injections of Hyalgan® (221 patients) 3 injections of Hyalgan® + 2 injections of placebo (218 patients) 5 injections of placebo (221 patients) Chronic shoulder pain	26	VAS pain scale	Pain reduction in treated groups until 26 weeks of follow-up	I
Kwon et al. 2013[76]	RCT	3 injections of Supartz® (150 patients) 3 injections of placebo (150 patients) Gleno-humeral osteoarthritis	26	VAS pain scale, responder percentages in OMER-ACT-OARSI	Significant improvement in pain and function for treated group compared to control group at all endpoints	I
Merolla et al. 2011[77]	Retrospective controlled	3 injections of Synvisc® (51 patients) 3 injections of 6-methylprednisone acetate (33 patients) Gleno-humeral osteoarthritis	24	VAS, Constant-Murley	Significant improvement in pain and function for treated group compared to control group at all endpoints ($p<0,05$)	III
Ozgen et al. 2012[78]	Perspective randomized	3 injections of Synvisc® (12 patients) Standard rehabilitative treatment (12 patients) Supraspinatus tendinopathy	4 years	VAS, ROM, SASES score	Significant improvement in both groups ($p<0,001$) without differences	II
Park et al. 2013[84]	Perspective randomized	2 injections with ND device (45 patients) 2 injections with ND corticosteroid (45 patients) Adhesive capsulitis	6	VNS, ROM	Significant improvement in both groups for pain, statistically better improvement in external rotation for HA ($p<0,001$)	II
Rovetta & Monteforte 1998[89]	Perspective randomized	8 injections of Hyalgan® + triamcinolone acetonide + exercise (15 patients) 8 injections of triamcinolone acetonide + exercise (15 patients) Adhesive capsulitis	24	VAS, ROM	Significant improvement in pain and function for treated group compared to controls at all endpoints ($p<0,001$)	II
Hsieh et al. 2012[90]	RCT	3 injections with ND device (35 patients) Physical therapies (35 patients) Adhesive capsulitis	12	SPADI, ROM, SF-36	Significant improvement in both groups ($p<0,001$) without differences	I

role of HA is not well established and limited in secondary osteoarthritis. Only two case series investigated HA in elbow osteoarthritis (Tab. IV)[96,97].
Level of recommendation: C.

Keypoints
- Low grade evidences support HA injections in elbow tendinopathies.

Table II. Selected studies of subacromial space injections

Author and year	Study design	Protocol/pathology	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Meloni et al. 2008[91]	RCT	5 injections of Hyalgan® (28 patients) 5 injections of placebo (28 patients) Supraspinatus tendinopathy	48	VAS pain scale	Significant improvement in pain and function for treated group compared to controls at all endpoints (p<0,001)	I
Chou et al. 2010[92]	RCT	5 injections of Artz® (25 patients) 5 injections of placebo (26 patients) Gleno-humeral osteoarthritis	2 years	VAS, Constant-Murley	Significant improvement in pain and function for treated group compared to controls at all endpoints (p<0,001)	I
Tagliafico et al. 2011[93]	Perspective, open-label	2 injections of high molecular weight HA ND (33 patients) Gruop that refused infiltrative therapy (60 patients) Massive rotator cuff lesion combined to advanced gleno-humeral osteoarthritis	24	VAS, Constant-Murley	Significant improvement in pain and function for treated group at 1, 2, 3 and 4 months follw-up, without statistical differences compared to controls at 6 months	III
Moghtaderi et al. 2013[29]	RCT	3 injections of Fermathron® (20 patients) 3 injections of placebo (20 patients) Rotator cuff tendinopathy	12	VAS, Constant-Murley	Significant improvement in pain and function for treated group compared to controls (p<0,001)	I
Merolla et al. 2013[30]	Perspective randomized	2 injections of SportVis® (25 patients) Standard rehabilitative treatment (23 patients) Supraspinatus tendinopathy	12	Oxford Shoulder Score, Constant-Murley Score	Significant improvement in pain and function for treated group from 2 to 12 weeks and in CS at 4 and 12 weeks compared to controls	II

- There are not sufficient evidences to recommend or avoid HA in primary and secondary elbow osteoarthritis.
- No adverse effects were observed with HA injections in patients affected by elbow pathologies.

KEY WORDS: hyaluronic acid, lateral epicondylitis, elbow osteoarthritis, elbow stiffness, elbow injection of hyaluronic acid, medial epicondylitis, hyaluronan elbow, sodium hyaluronate elbow.

Hyaluronic acid in hip disorders

Only few randomized controlled trials investigated the use of intra-articular injections of HA in hip osteoarthritis[98-105] and they are very heterogeneous for methodologies and type of HA used (Tab. V).

In a recent systematic review and meta-analysis, Piccirilli et al. concluded that HA represents a valid conservative therapeutic option for hip pathology, although there is lack of uniformity regarding choice of HA type, timing and number of injections[106].

Level of recommendation: B.

Keypoints

- Viscosupplementation is the best conservative treatment for osteoarthritis and it acts on pain reduction.
- Actually there is no uniformity regarding number or timing of infiltrative procedures.
- Ultrasound-guided infiltrative procedure is the best approach in terms of safety.
- In absence of comparative RCTs, no significant outcome differences seem to occur with different molecular weight HA formulations.
- Effectiveness on symptoms is only demonstrated in mild to moderate osteoarthritis, while infiltrative therapy is not indicated for severe forms of pathology.

Table III. Selected studies on epicondylitis.

Author and year	Study design	Protocol/pathology	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Petrella et al. 2010[94]	RCT	2 injections of HA ND (165 patients) 2 injections of placebo (166 patients)	48	VAS pain scale, gripping force with dynamometer, return to sport	Significant improvement in pain and function for treated group compared to controls at all endpoints (p<0,001)	I
Kumai et al. 2014[68]	Perspective, non randomized	1 injection of Suvenyl® (16 patients) Epicondylitis	1	VAS	Improvement ≥2 cm in VAS scale in 10 patients (62,5%)	IV
Tosun et al. 2015[95]	RCT	1 injection of Ialuril® (25 patients) 1 injection of triamcinolone acetonide (32 patients) Epicondylitis	12	VAS, PRTEE	Significant improvement in pain and function for HA+CS group at 3 months and in pain at 6 months compared to CS group	II

Table IV. Selected studies on elbow osteoarthritis.

Author and year	Study design	Protocol/pathology	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Van Brakel & Eygendaal 2006[96]	Case series	3 injections of Fermathron® (18 patients -19 joints) Post-thraumatic osteoarthrtis	24	VAS, EFA score, Broberg-Morrey Functional Rating Index	Slight non-significant improvement in pain and rigidity at 3 months	IV
Pederzini et al. 2013[97]	Case series	1 injection of Hyaloglide®+ arthrolysis (17 patients) Arthroscopic arthrolysis (19 patients) Post-thraumatic osteoarthrtis	10	VAS, ROM, Liverpool elbow score (LES)	Higher percentage of patients with pain reduction in HA group (p=0,0419), significant reduction in pain intensity in both gruops (p<0,0001)	IV

KEY WORDS: hyaluronic acid, hip injections, hip osteoarthritis, hip diseases.

Hyaluronic acid in knee disorders

Knee is the most studied application of HA injections and a common site of pathology, representing over 45% of total cases of symptomatic osteoarthritis. Several high-quality meta-analyses and review of RCTs were performed (Tab. VI).

Effects on symptoms

Intra-articular injections of HA lead to symptom relief comparable or superior to traditional treatments, such as intra-articular corticosteroids, NSAIDs, analgesics, lifestyle changes and physical exercise[107-112].

Level of recommendation: A.

Structural effects

Different studies have shown that the use of HA in knee osteoarthritis leads to structural improvements, including reduction of grade and extension of cartilage lesions, accompanied by decrease in synovial fluid inflammation, improvement in quantity and density of chondrocytes, increase in synovial repair processes[113-116].

Level of recommendation: A.

Effects on delay of prosthetic replacement surgery

Even if only few studies have been conducted on this topic, those carried out agree that repeated treat-

Table V. Selected studies on hip osteoarthritis.

Author and year	Study design	Protocol/pathology	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Tikiz et al. 2005[98]	RCT	3 injections of Synvisc® (25 patients, 32 hips) 3 injections of Ostenil® (18 patients, 24 hips) Fluoroscopic guide	24	VAS, WOMAC, Lequesne	Both treatments are effective without statistical differences	I
Qvistgaard et al. 2006[99]	RCT	3 injections of Hyalgan® (33 patients) 3 injections of placebo (36 patients) 1 injection of Depo-Medrol®+ 2 sham injections (32 patients)	12	VAS scale during walk	Significant pain reduction in CS group compared to placebo and HA at 14 and 28 days	I
Van den Bekerom et al. 2008[100]	Perspective, non randomized	1 injection of Adant® (91 patients) 1 injection of Synocrom® (20 patients) 1 injection of Synvisc® (15 patients) Fluoroscopic guide	6	VAS, Harris Hip Score	Significant improvement in pain and function for Adant e Synocrom groups	III
Richette et al. 2009[101]	RCT	1 injection of Adant® (42 patients) 1 injection of placebo (43 patients) Fluoroscopic guide	12	VAS	No significant differences between groups	I
Migliore et al. 2009[102]	RCT	2 injections of Hyalubrix® (22 patients) 2 injections of mepivacaine (20 patients) Ultrasound guide	12	VAS, Lequesne	Significant improvement in pain ($p<0,05$) and Lequesne ($p<0,001$) for HA group at all follow-up	I
Spitzer et al. 2010[103]	RCT	3 injections of Synvisc® (150 patients) 2 injections of metilprednisolone (155 patients) Fluoroscopic guide	26	WOMAC	HA is better than CS in advanced stages of pathology, same effectiveness in less advanced stages	I
Atchia et al. 2011[104]	Perspective, randomized	1 injection of Durolane® (19 patients) 1 injection di placebo (19 patients) 1 injection of corticosteroid (20 patients) Standard care (20 patients) Fluoroscopic guide	8	NRS, WOMAC	Significant improvement in pain and function for CS group	II
Battaglia et al. 2013[105]	RCT	3 injections of PRP (50 patients) 3 injections of Hyalubrix® (50 patients) Ultrasound guide	52	VAS, Harris Hip Score	Significant improvement in both groups ($p<0,005$) without differences at all follow-up	I

ments with HA infiltrations are effective in delaying total knee replacement surgery[117-120].

Level of recommendation: B.

Table VI. Selected studies on knee.

Author and year	Study design	Number of cases	Clinical evaluation	Results	Level of evidence
Day et al. 2004[108]	Multicentric, randomized, double blind	240 patients	6, 10, 14, 18 weeks VAS, WOMAC	Pain and articular stiffness reduction	I
Bannuru et al. 2011[109]	Review of RCTs	54 studies 7545 patients	4, 8, 12, 16, 20, 24 weeks WOMAC Meta-analysis	Maximum pain reduction at 8 weeks	I
Trigkilidas & Anand 2013[110]	Review of RCTs	14 studies 2289 patients	VAS, WOMAC	Maximum pain reduction at 6-8 weeks	I
Strand et al. 2015[111]	Review of RCTs	29 studies 4866 patients	From 4 to 13 and from 14 to 26 weeks Meta-analysis	Improvement in pain and function between 4 and 26 weeks	I
Waddell 2006[107]	Retrospective study	1158 patients	VAS, severity e duration of adverse event	Slight to moderate adverse events lasting less than 48 hours	III
Pasquali et al. 2001[115]	RCT	99 patients	7, 14, 21, 28, 35, 60, 120, 180 days Blood and urine tests 180 days Arthroscopy and biopsy	Reduction of inflamed tissue, improvement of edema, increase in fibroblasts and collagen	I
Navarro-Sarabia et al. 2011[114]	Multicentric, randomized, with blind assessor	306 patients	6, 12, 24 e 48 months VAS, OARSI criteria, OMERACT-OARSI criteria	Ripetitive cycles of intra-articular HA lead to an improvement lasting til one year after the end of treatment	I
Turajane et al. 2009[117]	Perspective study	183 patients	54 months of follow-up Incidence of TKR	Incidence of TKR of 28,4%	II
Waddell & Joseph 2016[118]	Review	1342 patients	13 years of follow-up Incidence of TKR	TKR delayed of 3 years in 25% of patients TKR delayed of 7 years in 75% of patients	I

Keypoints
- Knee infiltration with HA is strongly recommended for pain relief and potential disease-modifying effects.
- Evidence is greater for patients with mild to moderate osteoarthritis (K/L II-III).
- HA injections may delay the need for prosthetic knee replacement.

KEY WORDS: hyaluronic acid, molecular weight, knee, osteoarthritis, intra-articular injection, viscosupplementation, pain, tolerability, safety, meta-analysis, adverse events, total knee replacement.

Hyaluronic acid in ankle disorders

Hyaluronic acid is frequently used to reduce symptoms in early stages of ankle osteoarthritis. Many methods of treatment have been proposed, but actually no precise algorithm has been defined. HA is typically used when first-level analgesics have not determined adequate benefit and it could represent an option to postpone surgery[121,122].

In selected studies (7 studies; 5 RCTs) response to treatment was moderate even a large share of the samples respond to the treatment (Tab. VII)[123-129]. It remains unclear which patients (age, degree of ankle osteoarthritis) may have greater improvement from HA injections and the number of injections to perform per patient.

Level of recommendation: B.

Keypoints
- HA is safe in ankle joint, although improvements in clinical scores appear to be slightly significant in higher quality trials.
- HA can be recommended in patients who respond inadequately to common analgesics.
- It remains unclear which patients may have greater improvement from HA injections and the number of injections to perform per patient .

KEY WORDS: viscosupplementation, hyaluronic acid, ankle, arthritis.

Hyaluronic acid in small joints

The role of HA in small joints is not well established yet. Few studies investigated HA injections trape-

Table VII. Selected studies on ankle pathologies

Author and year	Study design	Protocol	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Salk et al. 2006[123]	RCT	5 injections of Hyalgan® (10 patients) 5 injections of placebo (10 patients)	24	AOS	Significant improvement in both groups (p<0,001)	I
Cohen et al. 2008[124]	RCT	5 injections of Hyalgan® (15 patients) 5 injections of placebo (15 patients)	12	AOS	Significant improvement in HA group compared to control group	I
Karatosun et al. 2008[125]	Perspective, randomized	3 injections of Adant® (15 patients) Exercise (15 patients)	52	AOFAS score, VAS pain	Significant improvement in both groups (p<0,001)	II
Carpenter et al. 2008[126]	Perspective, non randomized	Ankle arthroscopy + 3 injections of Synvisc® (14 patients) Ankle arthroscopy (12 patients)	48	10 points pain score scale	Significant pain reduction in comparison to controls	IV
Mei-Dan et al. 2012[127]	RCT	3 injections of Euflexxa® (15 patients) 3 injections of PRP (14 patients)	28	AOFAS	Significant improvement in both groups (p<0,001), higher for PRP group (p<0,05)	II
DeGroot et al. 2012[128]	RCT	1 injection of Supartz® (32 patients) 1 injection of placebo (32 patients)	12	AOFAS	Significant improvement in both groups (p<0,001)	I
Sun et al. 2014[129]	RCT	1 injection of Hyalgan® + exercise (37 patients) 1 injection of botulinum toxin (38 patients)	24	AOS	Significant improvement in both groups (p<0,001)	II

ziometacarpal (TMC) and first metatarsophalangeal joint (MTPJ) OA, while other small joints were not studied.

Trapeziometacarpal joint osteoarthritis
Studies selected have heterogeneous protocols and only two RCTs were found (Tab. VIII)[130-139]. Although some studies demonstrate a significant decrease in pain at a medium-term follow-up, no significant superiority compared to corticosteroid or placebo is emerged. A volume of 0.3 cm^3 injected for each injection seems to be ideal in order to reduce volume effect and post-injection pain[15].
Level of recommendation: B.

First metatarsophalangeal joint osteoarthritis
Only few studies were conducted, while a high quality RCT showed that an intra-articular injection of hylan G-F 20 is no more effective than placebo in reducing symptoms in people with symptomatic first MTPJ OA (Tab. IX)[140-142].
Level of recommendation: C.

Keypoints
- In TMC OA a significant superiority compared to corticosteroids or placebo is not emerged, while HA seems to lead to higher improvements in long-term follow-up.
- In first metatarsophalangeal joint, no high-quality study demonstrate the superiority of HA in comparison to corticosteroids or placebo.

KEY WORDS: carpometacarpal joint, trapeziometacarpal, thumb, hallux rigidus, rhizarthrosis, metatarsophalangeal joint, golfer's toe and or viscosupplementation, hyaluronic acid, intra-articular injection.

Hyaluronic acid in tendon and bursa
HA after flexor tendon repair surgery
HA has been widely used for topical application and injections after surgical repair of flexor tendons of the hand with the aim of promoting tendon sliding and preventing post-surgical adhesions. Many Authors have showed a lower granulation tissue formation with reduction of post-surgical adhesions, in part for reduced peritendinous inflammation. Four high-quality RCTs were found (Tab. X)[143-146]. HA products with higher molecular weight and longer half-life favor a greater permanence of HA into intrasynovial peritendinous space compared to native HA and low molecular weight formulations, ensuring greater clinical efficacy.
Level of recommendation: A.

Table VIII. Selected studies on injections in trapeziometacarpal joint.

Author and year	Study design	Protocol	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Figen Ayhan et al. 2009[130]	RCT	1 injection of Hylan G-F 20 (33 patients) 1 injection of saline solution (33 patients)	24	VAS, gripping force, Dreiser	Significant improvement in function (p=0,001), VAS pain (p=0,002), gripping force (p= 0,004) for HA group	I
Salini et al. 2009[131]	Perspective non randomized	1 injection of HA 800-1200 kDa (18 patients)	4	VAS, FANS consumpion, Dreiser, gripping force	Significant improvement in pain (p<0,001), function (p<0,004), force (p<0,001)	III
Di Sante et al. 2011[132]	Perspective non randomized	3 weekly injections of HA ND (31 patients)	24	VAS, Duruöz Hand Index	Significant improvement only in pain at 1 and 3 months, but no improvement at 6 months nor in function	III
Frizziero et al. 2014[133]	Retrospective non randomized	3 weekly injections of Hyalgan® (58 patients)	24	VAS, FANS consumpion, gripping force	Significant improvement in pain (p<0,001) and reduced FANS consumption (p<0,017)	IV
Roux et al. 2007[134]	Perspective randomized	Sinovial® 1 injection (14 patients) 2 injections (14 patients) 3 injections (14 patients)	12	VAS, Dreiser	Significant improvement in pain and function, without significant differences between groups	II
Heyworth et al. 2007[135]	RCT	2 injections Synvisc® (20) 1 injection of placebo + 1 injection of betamethasone acetate (22 patients) 2 injections of placebo (18)	26	VAS, gripping force, DASH	No significant differences between groups, even if there is a postitive trend for HA group after 4 weeks	I
Fuchs et al. 2005[136]	Perspective randomized	3 injections of Ostenil Mini® (28 patients) 3 injections of triamcinolone acetonide (28 patients)	26	VAS, gripping force	Pain resolution, improvement in articular movement more lasting for HA group	II
Ingenoli et al. 2010[137]	Case series	3 injections of Hyalubrix® (32 patients)	24	VAS, Dreiser, gripping force	Significant improvement in pain and local inflammation at short and medium term	IV
Bahadir et al. 2009[138]	Perspective randomized	3 injections of Ostenil® (20 patients) 1 injection of triamcinolone acetonide (20 patients)	48	VAS, Duruöz Hand Index, gripping force	No significant differences between groups at all follow-up	II
Stahl et al. 2005[139]	Perspective randomized	3 injections of Ostenil Mini® (26 patients) 3 injections of methyl-prednisolone (26 patients)	24	Pain, gripper, gripping force, Purdue Pegboard Test	Both treatment are effective, HA gruop shows higher improvement in gripping force and PPT	II

HA in trigger finger, entesopathies and bursitis

In two recent randomized clinical trials, ultrasound-guided infiltration of medium molecular weight HA has been proposed for the treatment of stenosing tenosynovitis of finger flexor tendons, with encouraging results[147-148].

Evidence on clinical efficacy for HA in human insertional tendon disorders is limited at four studies, although results are promising[68,94,149,150] (Tab. XI).

HA injections have also been proposed for the treatment of bursitis. Actually only two prospective studies without a control group are available, respectively on

Table IX. Selected studies on first metatarsophalangeal joint injections.

Author and year	Study design	Protocol	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Munteanu et al. 2011[140]	RCT	1 injection of Hylan G-F 20 (75 patients) 1 injection of placebo (76 patients)	24	Foot Health Status Questionaire	No significant differences between groups at all follow-up	I
Pons et al. 2007[141]	Perspective randomized	1 injection of Ostenil Mini® (20 joints) 1 injection of triamcinolone acetonide (20 joints)	11	VAS, AOFAS score	Significant difference in pain during movement and AOFAS score for HA group ($p<0,05$)	II
Petrella & Cogliano 2004[142]	Perspective non randomized	8 injections of HA ND (47 patients)	16	VAS, tiptoe walking pain, ROM, global patient satisfaction	Significant improvement in all outcome measures	III

Table X. Selected studies on flexor tendons tendon pathology.

Author and year	Study design	Experimental groups	Protocol/pathology	Follow-up	Outcome measures	Results	Level of evidence
Wiig et al. 2014[143]	RCT	PXL01 in (46 patients) (1,5-8,1 MDa, 15 mg/ml) Placebo (49 patients)	Injection between tendon and sheath and around sheath during surgery Surgical repair of hand areas I-II flexor tendons: adhesion prevention	Until 12 months	TAM, tip-bend distance, sensitivity, degree of tenolysis, gripping force	HA improves post-surgical recovery, with more pronounced difference 6 months after surgery	I
Özgenel & Etöz 2012[144]	RCT	High molecular weight HA (11 patiens) (1,0-2,9 MDa, 15 mg/ml) Placebo (11 patients)	1 injection during surgery, 2 injections at weekly intervals Hand area II flexor tendon injury: adhesion prevention	3 weeks, 3 months, long-term	TAM, TPM, functional outcome with Strickland grading system	No differences at 3 weeks, improvement in HA group at 3 months and long-term	I
Riccio et al. 2010[145]	RCT	Hyaloglide® (26 patients) Standard surgical release (19 patients)	Application of Hyaloglide® along the exposed tendon surface and in digital canal Adhesions recurrence after tenolysis of flexor tendons in hand zone II	30-60-90-180 days after surgery	TAM, QuickDASH, working days lost after surgery	Better recovery of TAM and faster return to work and daily life activities in HA group	I
Hagberg et al. 1992[146]	RCT	High molecular weight HA (4.0 Mda) Placebo (120 cases stratified in 6 classes)	Injection in tendon sheath after tenorraphia or tendon graft Adhesions after surgical repair of flexor tendons in hand zone II	4 months	TAM, extension deficit, DIPAM (active motion)	No significant effects of HA on recovery of TAM	I

Table XI. Selected studies on tendon and bursal pathologies.

Author and year	Study design	Experimental groups	Protocol/pathology	Follow-up	Outcome measures	Results	Level of evidence
Liu et al. 2015[147]	RCT	Medium molecular weight HA (18 cases) (0,8-1,17 Mda) cortisone (19 cases)	1 US-guided injection of HA 1 US-guided injection of cortisone Trigger finger (stenosing tenosynovitis)	3 weeks, 3 months	Quinnell scale Michigan scale (MHQ), VAS, TAM, gripping force	Better outcomes for both groups, different trend for MHQ (progressive increase for HA; increase at 3 weeks, decrease at 3 months for steroid)	I
Callegari et al. 2011[148]	RCT	Cortisone/lidocaine + medium molecular weight HA (0,8-1,2 MDa) (15 patients) Open surgical release (15 patients)	US-guided injection of cortisone/lidocaine and after 10 days of HA	3 weeks, 3-6-12 months	DASH, Satisfaction Visual Analog Scale (SVAS), VAS	Similar results between groups	I
Tosun et al. 2015[149]	RCT	HA + chondroitin sulphate + prilocaine (25 patients) Triamcinolone + prilocaine (32 patients) No control group	Single injection of 1.6 mL in an area of about 2 cm^2 immediately anterior and distal to the lateral epicondyle Lateral epicondylitis	3-6 months after injection	Pain and function with PatientRated Tennis Elbow Evaluation (PRTEE)	Pain and function significantly improved at 3 and 6 months in both groups, but better results for HA+CS group	II
Kumai et al. 2014[68]	Pilot study	High molecular weight HA (2.7 Mda) (61 patients) No control group	Single injection of HMW-HA near affected tendon/insertion Entheopathy (epicondylitis, patellar tendinopathy, insertional Achilles tendinopathy, plantar fasciitis)	1 week after injection	Spontaneous pain (VAS), 5 categories of local symptoms, caused pain	VAS reduction for all infiltrated sites and improvement of local caused pain	IV
Muneta et al. 2012[150]	Cohort study	- Low molecular weight HA+ lidocaine (50 patients)(9.0 Mda) No control group	Injection between posterior tendon surface and infrapatellar fat (patellar tendinopathy) or more painful point around tendon; repeated from 1 to 11 times spaced at least 1 week Patellar tendinopathy and anterior knee pain syndrome in athletes	6-88 months	Roles and Maudsley modified score (pain and practice of sport)	Slight increase in pain 1-2 days after injection, then improvement compared to previous condition. Most effective in patellar tendinopathy compared to other types of anterior knee pain	II

To be continued

Continue from **Table XI.**

Petrella et al. 2010[94]	RCT	- HA (165 patients) (molecular weight not specified) - saline solution (166 patients)	2 weekly injections in subcutaneous and muscular tissue 1 cm from lateral epicondyle Lateral epicondylitis	7-14-30-90-365 days	VAS, gripping force, global satisfaction, return to ADL and sport	Better results in HA group	I
Chen et al. 2014[152]	Cohort study	High molecular weight HA(6000 kDa) (10 patients) Low molecular weight HA (500-730 kDa) (10 patients) No control group	3 intrabursal injections after aspiration with lateral access, on a weekly basis Knee suprapatellar bursitis	1-2-3-4 weeks after first injection	Difference in protein concentration in synovial fluid before and after injection	Similar results in both groups	II
Chang et al. 2009[151]	Pilot study	Cortisone + medium molecular weight HA (22 patients)(940-1020 kDa) No control group	3 non-guided weekly injections with access at vertebral margin of the scapula between serratus anterior muscle and lateral thoracic wall Scapulothoracic bursitis	1-2-3 weeks and 3 months after first injection	VAS, Rubin scale	Pain reduction, no significant adverse events	IV

scapulo-thoracic bursitis[151] and on suprapatellar bursitis[152]; both studies reported significant improvements and Authors seem to encourage the use of HA in such conditions.
Level of recommendation: C.

Keypoints
- HMW-HA into intrasynovial peritendinous space should be proposed after surgical repair of flexor tendons of the hand with the aim of preventing adhesions and optimize recovery of motility and function.
- Currently, the use of HA in insertional tendon disease, trigger finger and bursitis is not strongly support by evidences, even reporting encouraging results without major side effects.

KEY WORDS: tendon, periarticular, tendinopathy and or hyaluronic acid, injection.

Combination therapy with HA
Association with corticosteroids
Several studies investigated combined therapy with corticosteroids in various pathologies, as knee osteoarthritis, stenosing tenosynovitis of fingers flexor tendons, internal derangement of temporomandibular joint, adhesive capsulitis and lateral epicondylitis (Tab. XII)[89,148,153-157]. Despite the different indications and protocols, all these studies suggested the superiority of the therapeutic association in terms of efficacy (pain reduction) compared to the use of each treatment alone.
Level of recommendation: B.

Association with local anesthetics
In the selected studies HA and local anesthetics have been used in association to other drugs, so it is difficult to establish the clinical efficacy of this combined therapy, whether the outcome was favorable for combined treatment groups[148,149,157].
Level of recommendation: C.

Association with NSAIDs
Only two RCTs analyzed the association between HA and NSAIDs. Both demonstrated a superiority in terms of pain reduction for combined intra-articular therapy compared to HA alone in subjects suffering of knee OA[158,159].
Level of recommendation: C.

Association with PRP
A retrospective non-randomized clinical trial on patients affected by Kellgren-Lawrence grade III-IV knee OA showed better outcome for the group treated with association between HA and PRP compared to HA alone[160].
Level of recommendation: C.

Association with MSCs
A recent RCT showed an increased quality of articular cartilage tissue after associative treatment with HA and peripheral blood stem cells compared to HA alone in patients with chondral lesions of the knee[161].
Level of recommendation: C.

Table XII. Selected studies on combination therapies.

Author and year	Study design	Population	Treatments	Type of HA	Type of cotherapy	Follow-up period	Level of evidence
Callegari et al. 2011[148]	RCT	30 patients with stenosing tenosynovitis of fingers flexor tendons	2 groups: - corticosteroids + HA (group A) - open surgery (group B)	1 ml 0.8% of HA (Sinovial Mini)	Methylpredni-solone acetate 40 mg/1 ml (Depo-medrol)	6 weeks, 3, 6, 12 months	II
De Campos et al. 2013[153]	RCT	104 patients with gonarthrosis	2 groups: - 1 injection of HA (VS group); - 1 injection of HA + triamcinolone (VS+T group).	6 ml of Hylan GF-20	1 ml/20 mg of triamcinolone hexacetonide	1, 4, 12, 24 weeks	I
Giombini et al. 2016[162]	RCT	70 subjects with gonarthrosis	3 groups (1 injection/ week for 5 weeks): - HA only (n = 23); - only O^2O^3 (n = 23); - HA+O^2O^3 (n = 24)	20 mg/2 ml of HA (Hyalgan®)	mixture of O^2O^3 (15 ml) with [O3] of 15 µg/ml, obtained through an ozone generator	2 months from end of treatment	II
Giraddi et al. 2015[154]	RCT	14 patients with internal derangement of temporomandibular joint	2 groups (arthrocentesis + injection): - betamethasone + HA - only betamethasone	0.5 ml of HA	- group I: 0.5 ml of betamethasone; - group II: 1 ml of betamethasone	2 days, 1, 2 weeks, 1, 2, 6 months	II
Lee et al. 2011[158]	RCT	43 subjects with gonarthrosis	2 groups: - HA+30 mg of ketorolac (3 weeks), followed by HA alone (2 weeks) - only HA for 5 weeks	2.5 ml (1%) of Hyal (940-1020 kDa)	30 mg of ketorolac	1, 3, 5, 16 weeks after beginning of therapy	II
Ozturk et al. 2006[155]	RCT	40 patients with gonarthrosis	2 groups (3 weekly injections for 3 weeks+3 injections at 6th month): - HA (n = 24, group A); - HA + triamcinolone at I and IV injection	2 ml of HA (Orthovisc): 15 mg sodium hyaluronate +9 mg sodium chloride/1 ml	1 ml triamcinolone acetonide (Kenacort-A)	1-3, 6, 7, 9, 12 months	II
Palmieri et al. 2013[159]	RCT	62 patients with bilateral gonarthrosis	3 groups: - 66 mg of HA - 49.5 mg of HA + 5 mg of diclofenac - 49.5 mg of HA + 5 mg of sodium clodronate	- 66 mg/2 ml of HA (Variofill®) - 49.5 mg/1.5 ml of HA (Variofill®)	- 5 mg/0.5 ml of sodium diclofenac; - 5 mg/0.5 ml of sodium clodronate	3 and 6 months	II
Petrella et al. 2015[156]	RCT	98 subjects with gonarthrosis	3 groups: - HA (Hydros) - HA + 10 mg of triamcinolone acetonide (Hydros TA) - HA (Synvisc-One)	-Hydros -Hydros TA (HA + 10 mg triamcinolone acetonide) -Synvisc-One® (hylan G-F 20)	10 mg of triamcinolone acetonide	2, 6, 13, 26 weeks	II
Rovetta & Monteforte 1998[89]	RCT	30 subjects with adhesive capsulitis	2 groups (injections every 15 days in first month, then monthly for 6 months): - injection of HA + steroids + physiotherapy - injection of steroids + physiotherapy	20 mg of sodium hyaluronate	20 mg of triamcinolone acetonide (both groups)	6 months	II

To be continued

Continue from **Table XII.**

Saw et al. 2013[161]	RCT	50 patients with chondral lesions of the knee (grade 3-4 ICRS International Cartilage Repair Society)	2 groups (5 weekly injections, started 1 week after arthroscopy + 3 weekly injections after 6 months): - HA only - HA + peripheral blood stem cells (PBSC)	2 ml of HA for each injection	8 ml injection of PBSC	-IKDC: 6, 12,18,24 months -MRI: 6, 12,18 months -biopsy: 18 months	II
Tosun et al. 2015[149]	RCT	57 patients with clinical diagnosis of lateral epicondylitis	2 groups (1 single injection): - HA + chondroitin sulfate (CS) + prilocaine - triamcinolone + prilocaine	1 ml of Ialuril (800 mg of HA +1 g of chondroitin sulphate/50 ml)+0.6 ml of prilocaine HCl (Citanest)	1 ml triamcinolone acetonide (40 mg/ml, Kenacort-A Retard) + 0.6 ml of prilocaine HCl (Citanest)	3 and 6 months after injection	II
Saturveithan et al. 2016v	Retrospective non randomized	64 patients (101 knees) with gonarthrosis	2 groups: - HA + PRP (56 knees) - HA only (45 knees)	4 ml of high-MW HA (1476x106 Da) with a concentration of 22 mg/ml	2.5-3 ml of PRP with an average [PLTs] of 1.4-1.6 million/µl	2 and 6 months after injection	II
Briggs et al. 2012[157]	Clinical trial without control	47 patients (27 females) with diagnosis of gonarthrosis	Cycle of 3 injections: - at I injection brand+ HA+Kenalog+lidocaine - at II and III injection only HA	Hylan G-F	- 2 ml of Kenalog-10 (triamcinolone acetonide); - 3 ml of brand (Bupivacaine) - 3 ml of lidocaine	3, 6, 12 weeks and 6 months	III
Conrozier et al. 2016[163]	Retrospective clinical trial without control	40 patients with gonarthrosis	1 single injection of HAnox-M-XL (4.4 ml)	HAnox-M-XL 4.4 ml: cross-linked HA (16 mg/ml) + mannitol (35 mg/ml)	35 mg/ml of mannitol	3 and 6 months	III
Henrotin et al. 2012[164]	Clinical trial without control	30 patients with gonarthrosis	3 weekly injections of sterile solution (2 ml) of HA+chondroitin sulphate (CS)	24 mg of HA	60 mg chondroitin sulfate (Structovial CS)	6 and 12 weeks	III

Association with other drugs/medical devices
Three different studies reported significant clinical benefits with the use of HA in association to oxygen-ozone therapy, mannitol and chondroitin sulfate, respectively, in patients with knee osteoarthritis[162-164].
Level of recommendation: C.

Keypoints
- The association of HA with other drugs or devices could have advantages in comparison to HA alone.
- Dosage and frequency of association with HA in osteoarticular and myotendinous diseases are not defined.
- Future high quality RCTs are needed in order to improve the knowledge about mechanism of action and efficacy of combined therapies.

KEY WORDS: hyaluronic acid, musculoskeletal, injection, intra-articular, sodium hyaluronate, anesthetic, corticosteroid, NSAIDS, PRP, mesenchymal stem cells, ozon.

Ultrasound guidance for HA injection in musculoskeletal disorders
The advantages of ultrasound (US) imaging (real-time execution, absence of ionizing radiation, low cost and availability of device) are responsible of the large diffusion of US-guidance.

US-guidance in shoulder pathologies
Three studies were selected. Two studies investigated the outcome in patients with adhesive capsulitis[84,165], while one study in subacromial pain syndrome (Tab. XIII)[166]. All studies reported good clinical results after US-guided injections of HA, at least in the short term.
US-guidance in hand pathologies
Four different studies shave reported that US-guided injections of HA appear to be a safe and suitable tool

Table XIII. Selected studies for on US-guided injections.

Author and year	Population	Type of HA	Injection frequency	Follow-up period	Level of evidence
Atchia et al. 2011[104]	77 patients with unilateral coxarthrosis waiting for surgical total hip replacement	3 ml/60 mg of Durolane	Not specified	1, 4, 8 weeks	II
Battaglia et al. 2013[105]	100 patients with unilateral coxarthrosis	High molecular weight HA (1500 Kd, Hyalubrix)	3 consecutive injections (every 2 weeks)	1, 3, 6, 12 months	I
Bum Park et al. 2012[169]	99 subjects with gonarthrosis	2 ml 1% high molecular weight HA (940-1020kDa)	3 weekly intra-articular injections	-	II
Callegari et al. 2011[148]	30 subjects with stenosing tenosynovitis of finger flexors	1 ml 0.8% HA (Sinovial Mini) +methylprednisolone acetate 40 mg/1 ml (Depo-medrol)	2 injections (10 days between them)	6 weeks, 3, 6, 12 months	II
Kim et al. 2012[166]	80 patients with subacromial conflict syndrome	2 ml/20 mg of Hyruan plus (average molecular weight 300,000,000 Da)	3 weekly injections (AI group); 1 injection (corticosteroid group)	3, 6, 12 weeks	II
Lee et al. 2009[165]	43 patients with shoulder adhesive capsulitis	2.5 ml/25 mg of low molecular weight HA	I week: 0.5 ml/20 mg of triamcinolone with 1.5 ml of 2% lidocaine and 3 ml of saline solution; II-VI week: HA	Weekly follow-up	II
Liu et al. 2015[147]	36 subjects (39 fingers) with clinical diagnosis of trigger finger	1 ml medium molecular weight HA(1000-1200 kDa, Artz)	1 injection	3 weeks, 3 months	II
Monfort et al. 2015[168]	88 patients with rhizoartrosis	0.5 cm3/5 mg of 500-1000kDa HA produced by bacterial fermentation (Suplasyn®)	3 weekly injections	7,14,30,90, 180 days	II
Orlandi et al. 2015[167]	75 patients with unilateral de Quervain's disease	16 mg/2 ml of low molecular weight HA (0.8%, Sinovial)	2 injections (15 days between them): I injection: steroid; II injection: HA	1, 3, 6 months	I
Park et al. 2013 [84]	90 patients with shoulder adhesive capsulitis	18 ml of lidocaine 0.5% for capsular distention + 2 ml high MW HA (10 mg/ml)	3 biweekly injections	2 and 6 weeks	II
Qvistgaard et al. 2006[99]	101 patients with coxarthrosis	2 ml of HA (Hyalgan®)	3 injections every 14 days	14, 28, 90 days	II

for the treatment of trigger finger, de Quervain's disease and rhizarthrosis[147,148,167,168].

US-guidance in hip

US-guided injections of HA have shown good results in three studies on patient with hip osteoarthritis[99,104,105]. Authors suggested that US could be useful not only as a guide, but also as a biomarker of response to therapy.

US-guidance in knee

One level II study reported that the precision of injection is better for US-guided procedure in comparison to anatomical landmark injections in suprapatellar bursitis[169].

Level of recommendation for US-guided injection in hip joint: A.

Level of recommendation for US-guided injection in trigger finger: B.

Level of recommendation for US-guided injection in rhizarthrosis, glenohumeral joint and subacromial space: C.

Level of recommendation for US-guided injection in other anatomical sites: D.

Keypoints
- Ultrasound imaging is an effective tool for intra-articular injections guidance in several musculoskeletal disorders, in absence of contraindications and severe side effects.
- While US offers various advantages (cost/benefit ratio, availability, real time acquisition), there is still lack of strong evidence regarding the impact of HA injections with ultrasound guidance in terms of accuracy and benefits in comparison to blinded procedures.

KEY WORDS: hyaluronic acid guided injection as mesh term.

Hyaluronic acid and exercise therapy
Four RCTs[125,170-172] and one review[174] compared the effectiveness of intra-articular injections of HA to a specific rehabilitative protocol in the treatment of patients with knee and ankle osteoarthritis; only one RCT investigated the combination to each treatment in alone (Tab. XIV).
The results lead Authors to conclude that both treatments improve pain and function, although combined treatment seems to guarantee greater efficacy, at least in the short term.
Level of recommendation: B.

Keypoints
- Both HA injections and exercise therapy alone and in combination should improve pain e function in patients affected by OA.
- A single RCT suggested a possible greater efficacy of combined treatment in the short term.
- More studies are needed to strongly support this recommendation.

KEY WORDS: hyaluronic acid injection, physical exercises, exercise therapy, viscosupplementation, rehabilitation protocol and/or randomized controlled trial, systematic review.

Hyaluronic acid and physical therapies
In clinical practice the association between HA injection and physical therapies is common. Indeed, the effects of these therapies seem to be complementary and synergistic: in particular, physical therapies show beneficial actions in the acute phase reducing pain and inflammation through thermal, biochemical, mechanical and electrical effects, while HA acts mainly by facilitating and maintaining functional recovery over time.
However, the real effectiveness of physical therapies in musculoskeletal pathologies is controversial and only few scientific studies are aimed at validating the association between them and HA.

Osteoarthritis
Three studies[6,23,25] show better results with the association of HA and physical therapies compared to physical therapies alone in patients with shoulder and knee osteoarthritis[174-176] (Tab. XV). One pilot study did not show any significant difference, even both short-term (3 weeks) and long-term (3 months) evaluations, index of severity for osteoarthritis of the knee scores were reduced in all three groups[177].

Adhesive capsulitis
Two studies[26,27] agree that the addition of HA to conventional treatments (including physical therapies) does not add significant benefits in patient suffering from adhesive capsulitis.
Level of recommendation: C.

Keypoints
- HA and physical therapies are commonly used for the treatment of musculoskeletal pathologies.
- Evidence on the effectiveness of physical therapies in joint and tendon disorders is controversial, mainly because of the lack of high quality RCTs.
- Only few studies demonstrated the effectiveness of association between physical therapies and HA, especially in knee and shoulder osteoarthritis, while there is no evidence on shoulder adhesive capsulitis.

KEY WORDS: hyaluronic acid injection, physical therapy, lasertherapy, viscosupplementation, rehabilitation protocol, shockwaves, ultrasound, electrotherapy and/or randomized controlled trial, systematic review.

Hyaluronic acid in post-surgical management
The promising results obtained in the conservative treatment of various musculoskeletal diseases have led many surgeons to propose HA also in post-surgical management, especially after shoulder, knee and ankle arthroscopy (Tab. XVI).

HA after knee arthroscopy
Early viscosupplementation in arthroscopic partial meniscectomy was found to have conflicting results and a possible improvement in short-term pain is not showed in all level I studies[178-180].
Different studies on viscosupplementation after ACL reconstruction evidenced inflammation, swelling and pain reduction only in the immediate post-operative period, without any difference in the long-term[69,181,182].
Conversely, three RCTs showed significant pain and clinical scores improvement for HMW HA after knee arthroscopy in knee OA[183-185].

HA after shoulder arthroscopy
Postoperative capsular stiffness is the main complication after shoulder arthroscopy and may determine prolonged rehabilitation period. HA could be used in post-surgery with the aim of decreasing adhesions and thus facilitating rehabilitation.
However, a recent RCT has not showed significant difference in pain VAS, internal rotation, external rotation and functional scores between two groups at each follow-up period[186].

Table XIV. Selected studies on HA and exercise.

Author and year	Study design	Protocol	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Karatosun et al. 2006[170]	Randomized	3 injections of Hylan G-F20 (52 patients) Exercise (53 patients)	12,24,48,72	Hospital for Special Surgery (HSS) Knee Score	No differences between groups	II
Karatosun et al. 2008[125]	Randomized perspective	3 injections of Hylan G-F 20 (19 patients) Exercise (24 patients)	8,12,24,48	American Orthopedic Foot and Ankle Society (AOFAS) score, VAS score	No differences between groups	II
Kawasaki et al. 2009[171]	Randomized perspective	1 injection of ND device (42 patients) Exercise (45 patients)	24	VAS, Japanese Knee Osteoarthritis Measure (JKOM)	No differences between groups	II
Saccomanno et al. 2016[172]	Randomized	3 injections of Orthovisc (55 patients) Exercise (55 patients) 3 injections of Orthovisc + Exercise (55 patients)	4,12,24	Western Ontario and McMaster Universities (WOMAC) Index, Active Range of Movement (AROM)	Significant improvement in pain at 1 month in HA + exercise group	I

Table XV. Selected studies on combined HA and physical therapies.

Author and year	Study design	Protocol/pathology	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Di Giacomo & De Gasperis 2015[174]	Randomized perspective	5 injections of Hyalgan 20 + exercise (31 patients) Physical therapies (30 patients) Glenohumeral osteoarthritis	16, 24	Constant scale	First group (HA+PT) had statistically better results on disability and pain compared to second group (PT)	II
Huang et al., 2005[175]	Randomized	Injection of ND device + exercises + US (32) Exercises (26) Exercises + US (29) Control (31) Gonarthrosis	8, 1 year	Lequesne scale, VAS, ROM, walking speed, peak of strength	Combined treatment with HA, isokinetic exercises and US gave better results on disability and pain compared to exercises alone or exercises + US at 1 year	II
Bayramoğlu et al., 2003[177]	Randomized	3 injections of Synvisc® + exercise (12 patients) 3 injections of Orthovisc® + exercise (16 patients) Exercise (9 patients) Gonarthrosis	3,12	Lequesne scale, isokinetic strength	No significant differences in function at 3 weeks and 3 months between treatment with HA+PT (TENS + diathermy) and PT alone	II
Ip & Fu 2015[176]	Randomized perspective	Exercise + fake irradiation + 5 injections of saline solution (70 patients) Exercise + 5 injections of Hyalgan® +LLLT (70 patients) Gonarthrosis	7 years	WOMAC scale, use of prosthesis	Group B treated with LLLT + low molecular weight HA had greater reduction of pain and minor recourse to prosthetic surgery compared to group A treated with traditional physical therapies like US, ET and diathermy	II

Table XVI. Selected studies on post-surgical management.

Author and year	Study design	Protocol/pathology	Follow-up (weeks)	Outcome measures	Results	Level of evidence
Mathies 2006[178]	RCT	25 patients: treatment 25 patients: control Arthroscopic meniscectomy	4	VAS, circumference	Less pain and swelling in the first 30 days	I
Thein et al. 2010[179]	RCT	28 patients: treatment 28 patients: control Arthroscopic meniscectomy	12	VAS, circumference	Less pain, less swelling, equal functional scores	I
Filardo et al. 2016[180]	RCT	45 patients: treatment 45 patients: control Arthroscopic meniscectomy	24	IKDC, KOOS, VAS, Tegner scores	No difference	I
Heybeli et al. 2008[183]	RCT	33 patients: treatment 34 patients: control Gonarthrosis	24	WOMAC, VAS	Better clinical scores at 6 weeks No difference at 24 weeks	I
Westrich et al. 2009[184]	RCT	23 patients: treatment 23 patients: control Gonarthrosis	24	VAS, functional results	Better results for treatment group	I
Hempfling 2007[185]	RCT	40 patients: treatment 40 patients: control Gonarthrosis	2 years	VAS, walking ability, functional results	Better results in treatment group	I
Huang et al. 2007[69]	RCT	90 patients: treatment 30 patients: control LCA reconstruction	16	Lysholm scale, ROM, walking speed	Better results in treatment group	I
Chau et al. 2012[181]	RCT	16 patients: treatment 16 patients: control LCA reconstruction	12	KOOS, ROM, circumference, use of analgesics	Improvement in pain and swelling at 2 days	I
Di Martino et al. 2016[182]	RCT	30 patients: treatment 30 patients: control LCA reconstruction	1 year	ROM, VAS, circumference, SF-36, IKDC, Tegner score	Improvement in ROM and swelling at 30 and 60 days	I
Oh et al. 2011[186]	RCT	40 patients: treatment 40 patients: control Rotator cuff suture	1 year	VAS, ROM, CONSTANT, ASES	No difference	I
Doral et al. 2012[187]	RCT	41 patients: treatment 16 patients: control Chondral lesions of astragalus	2 years	Freiburg, AOFAS score	Better results for treatment group	I
Görmeli et al. 2015[188]	RCT	13 patients: PRP 14 patients: HA 13 patients: control Chondral lesions of astragalus	60	AOFAS score, VAS	Better results in PRP and HA groups compared to controls	I

HA after foot and ankle surgery
Two different level I RCTs showed that HA in addition to microfractures could offer better clinical results in osteochondral lesions of the talus[187,188].
Level of recommendation: A after knee arthroscopy in knee OA patients.
Level of recommendation: D after knee arthroscopic meniscectomy and ACL surgery.
Level of recommendation: A in post-surgical pain management.
Level of recommendation: C after shoulder arthroscopy and foot and ankle surgery.

Keypoints
- HA may determine improve in pain in the early post-operative period after knee artrhoscopy.
- HA does not appear to offer any long-term clinical benefit after arthroscopic meniscectomy and LCA surgery.
- Further studies are needed to recommend the use of HA after shoulder and ankle surgery.

KEY WORDS: hyaluronic acid, viscosupplementation, sodium hyaluronate, knee arthroscopy, knee surgery, shoulder arthroscopy, shoulder surgery, ankle arthroscopy, ankle surgery, ligaments and tendons, tendon surgery.

Contraindications and adverse effects
Fifty-seven studies (40 RCTs and 17 systematic reviews) were selected[65,78,98,99,101,102,104,107,108, 114,136,139, 140,148,156,158,159,189-227].
Absolute contraindications are represented by hypersensitivity to products, suspect or presence of infections at injection skin site or selected joint, joint inflammatory states.
As intra-articular injection represents an invasive procedure, should be carefully considered in patients suffering from hematological disorders.
Hepatic pathologies and venous and/or lymphatic stasis could affect HA metabolism.
Considering the lack of scientific evidence regarding HA safety in pregnancy, breast-feeding and in the pediatric population, viscosupplementation is contraindicated in these conditions (Tab. XVII).
Adverse effects are of minor entity, as usually not limit daily life activities and disappear in a few hours or days (Tab. XVIII).
Minor adverse effects include local superficial or articular pain and/or swelling, myalgia, upper respiratory tract disorders, headache, paresthesia, lipothymia, gastrointestinal minor disorders, general fatigue, skin rash, local pruritus, urticaria, allergic manifestations, phlebitis and other minor events.
Only few studies reported more serious adverse events that however concerned a negligible percentage of included subjects and were considered improbable and unrelated to the treatment.
Level of recommendation: A for safety and tolerability of HA products.

Keypoints
- HA injections are well tolerated.
- Adverse effects due to HA injections are not frequent, minor and transient; serious adverse events recorded were not related to treatment.

KEY WORDS: hyaluronic acid injection, side effects, contraindication.

Authors contributions

I.S.Mu.L.T. - ITALIAN SOCIETY OF MUSCLES LIGAMENTS & TENDONS. Italian version of the Guidelines: “Linee Guida I.S.Mu.L.T. Trattamento infiltrativo con acido ialuronico nelle patologie dell’apparato muscolo-scheletrico” IBSA Farmaceutici Italia, Edra Editore, 2017.

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Table XVII. Contraindications reported on leaflets of each HA formulation considered.

Trade name	Hyper-sensitivity to HA	Skin infections	Joint infections	Joint phlogosis	Pregnancy /lactation	Lymphatic/ venous stasis	Liver patho-logies	Pediatric age	Blood disorders
Artrhum	0	0	0	0	0	0	0	0	0
Arthrum 2.5%	0	0	0	0	0	0	0	0	0
Artrosulfur HA	0	1	1	1	0	0	0	0	0
Artz/Supartz	1	0	0	0	1	0	1	1	0
Condrovisc	0	1	1	1	1	0	0	0	0
Coxarthrum	1	0	1	1	0	0	0	0	0
Durolane (AF)	0	1	0	0	1	0	0	1	0
Euflexxa	1	1	1	0	1	0	0	0	0
Fermathron (AF)	1	1	1	0	0	0	0	0	0
Go-on	1	0	0	1	0	0	0	0	0
Go-on Mini	1	0	0	1	0	0	0	0	0
Go-on matrix	1	1	1	1	0	1	0	0	0
Hyalart	1	0	0	0	0	0	1	0	0
Hyalgan	1	0	0	0	0	0	1	0	0
Hyalubrix	1	1	0	0	0	0	0	0	0
Hyalubrix 60*	1	1	0	0	0	0	0	0	0
Hymovis	1	1	0	0	0	0	0	0	0
Inartral	1	1	0	0	0	0	0	0	0
Intragel (AF)	0	1	1	1	0	0	0	0	0
Jointex (AF)	0	1	1	1	0	0	0	0	0
Jonexa	1	1	1	0	0	1	0	0	0
Kartilage (AF)	1	0	0	1	0	0	0	0	0
MonoVisc	1	1	0	0	0	0	0	0	1
OrthoVisc (AF)	1	0	0	0	1	0	0	0	0
Ostenil (AF)	1	0	0	0	0	0	0	0	0
Proial	1	1	1	0	0	0	0	0	0
Promovia	0	1	0	0	0	0	0	0	0
RenehaVis	1	0	0	0	0	0	0	0	0
Rhizarthrum	1	0	1	1	0	0	0	0	0
Sinovial (AF)	0	1	1	1	0	0	0	0	0
SportVis	1	1	0	0	0	0	0	0	0
Structovial	1	0	1	0	0	0	0	0	0
Synocrom (AF)	1	0	1	0	0	0	0	0	0
Synolis V-A	1	1	1	0	1	0	0	1	0
Synvisc (AF)	0	1	1	1	0	1	0	0	0
Yaral (AF)	0	1	1	1	0	0	0	0	0
Viscoplus (AF)	0	0	0	0	0	0	0	0	0

Notes: * also Hyalone; AF: all formulations of the same brand.

Table XVIII. Adverse events reported in selected studies after HA injection.

Author and year	Study design	Population	Treatments	Type of HA	Adverse events	Level of evidence
Abate et al. 2008[189]	Systematic review	17 clinical trials (coxarthrosis)		No difference between HA formulations (data not shown)	- pain at injection site - heaviness at injection site	I
Altman et al. 1998[192]	RCT multicenter	495 patients with idiopathic gonarthrosis	3 treatment groups: - HA - placebo - naproxen	2 ml/20 mg Hyalgan	- pain at injection site - gastrointestinal disorders - swelling/effusion - death (pre-existing cardiovascular disorders)	I
Altman et al. 2009[193]	RCT	588 subjects with gonarthrosis	2 groups: - Phosphate Buffered Saline (PBS) - BioHA	20 mg/2 ml of EUFLEXXA® (1% bio-engineered sodium hyaluronate)	- pain at injection site - arthralgia - pneumonia - TIA	I
Altman et al. 2011[194]	RCT	433 subjects with gonarthrosis	2 groups: - PBS - BioHA	20 mg/2 ml of EUFLEXXA® (1% bio-engineered sodium hyaluronate)	- pain at injection site - arthralgia - rhinopharyngitis - other upper airways infections - soft tissue edema adjacent to injection site - joint swelling - peripheral edema	I
Arden et al. 2014[195]	RCT	208 patients with gonarthrosis	2 groups: - 3 ml of NASHA (Not Animal Stabilized HA) - 3 ml of saline solution buffered at pH 7	60 mg/3 ml of Durolane (NASHA with unique cross-linked molecular structure)	pain at injection site	I
Arrich et al. 2005[196]	Systematic review	22 studies (gonarthrosis)		Hyalgan 500-730 kDa Orthovisc 1000-2900kDa HA nms 600-1200 kDa Artz 600-1200 kDa Artzal ~ 1000 kDa Synvisc ~ 7000 kDa Suplasyn 500-730 kDa BioHy 2400-3600 kDa	pain at injection site	I
Atchia et al. 2011[104]	RCT	77 patients with unilateral coxarthrosis waiting for total hip arthroplasty	4 groups: - standard treatment (without infiltrations) - saline solution - NASHA - methylpre-dnisolone acetate (Depomedrol)	3 ml/60 mg of Durolane	post-arthroplasty infection	I
Bannuru et al. 2014[197]	Systematic review	5 studies (gonarthrosis)		Synvisc, Hyalgan, Suplasyn, Suvenyl	- pain at injection site - TIA - myocardial infarction	I
Bellamy et al. 2005[198]	Cochrane review	63 trials (gonarthrosis)		Hyaluronate and hylan derivates (Adant, ArthrumH, Artz: Artzal, Supartz), BioHy (Arthrease), Durolane, Fermathron, Go-On, Hyalgan, Hylan G-F 20 (Synvisc Hylan G-F 20), NRD-101, Orthovisc, Ostenil, Replasyn, SLM-10, Suplasyn, Synject and Zeel compositum	- pain at injection site - joint swelling - gastrointestinal disorders - hemarthrosis - phlebitis - skin rash - pruritus	I

To be continued

Continue from **Table XVIII.**

Blaine et al. 2006[65]	RCT	660 subjects with shoulder pain	3 groups: - 5 infiltrations of HA - 3 infiltrations of HA + 2 of saline solution - 5 infiltrations of saline solution	2 ml Hyalgan (10 mg/ml)	- pain at injection site - arthralgia - rhinopharyngitis - headache - vertebral pain	I
Brandt et al. 2001[200]	RCT	226 patients with gonarthrosis	2 groups: - HA - salin solution	2 ml (15 mg/ml) of ORTHOVISC, high MW hyaluronic acid, extract from cock's crests	- pain at injection site - arthralgia - local inflammation - bruising - generalized fatigue - gastrointestinal diseases	I
Brzusek et al. 2008[201]	Systematic review	16 studies (gonarthrosis)		Euflexxa, Orthovisc, Hyalgan,Supartz,Synvisc	- pain at injection site - joint swelling	I
Callegari et al. 2011[148]	RCT	30 subjects with stenosing tenosynovitis of finger flexor	2 groups: - group A: corticosteroids + HA - group B: open surgery	1 ml 0.8% HA (Sinovial Mini) + methyl prednisolone acetate 40 mg/1 ml (Depo-medrol)	No adverse events	I
Chang et al. 2013[216]	Systematic review	9 studies (ankle osteoarthritis)		Not specified	- post-injection pain - increase in volume of inguinal lymph nodes - localized pruritus - dissecans osteochondritis (4 months after treatment)	I
Chevalier et al. 2010[202]	RCT	253 patients with gonarthrosis	2 groups: - arthrocentesis + infiltration of HA - arthrocentesis + injection saline solution	6 ml of Hylan G-F 20 (Synvisc-One)	- pain at injection site - joint stiffness - intraarticular effusion - joint swelling	I
Lee et al. 2011[158]	RCT	43 subjects with gonarthrosis	2 groups: - HA + 30 mg ketorolac (3 weeks), followed by HA alone (2 weeks) - HA alone for 5 weeks	2.5 ml (1%) of Hyal (MW: 940-1020 kDa)	- pain at injection site (HA+ketorolac group)	I
Day et al. 2004[108]	RCT multicentric study	223 patients with gonarthrosis	2 groups: - HA in saline solution - only saline solution	25 mg of ARTZ (extract from cock's crest, MW 6.2×105-11.7×105 Da)	pain at injection site	I
Diracoglu et al. 2009[222]	RCT	63 patients with bilateral gonarthrosis	2 groups: - HA - placebo	Hylan G-F 20 (Synvisc)	No adverse events	I

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Continue from **Table XVIII.**

Espal-largues et al. 2003[203]	Systematic review	14 studies (gonarthrosis)		Hylan G-F 20	- pain at injection site - muscle cramps - hemorrhoids - impatience	I
Fernández López et al. 2006[224]	Systematic review	8 studies (coxarthrosis)		Not specified	No adverse events	I
Filardo et al. 2012[204]	RCT	109 patients with knee chondropathy or gonarthrosis	2 groups: - PRP - HA	Hyalubrix (HA with MW > 1500 KDa)	pain at injection site	I
Fuchs et al. 2005[223]	RCT	60 patients with chronic non radicular lumbar pain	2 groups: - HA - triamcinolone acetonide	10 mg of Ostenil® mini, highly purified HA, from bacterial fermentation, in 1 ml of saline solution	No adverse events	I
Fuchs et al. 2006[136]	RCT	56 patients with rhizarthrosis	2 groups: - HA - triamcinolone acetonide	10 mg/1 ml of Ostenil® mini (1,2 MDa)	- lipotimia - pain at index finger - sciatica - pulmonary carcinoma	I
Oh et al. 2011[186]	RCT	80 subjects submitted to rotator cuff surgical repair	2 groups: Al/carboxymethylated cellulose no treatment	5 g of HA / carboxymethylated cellulose (CMC): Guardix-Sol®	No adverse events	I
Ishijima et al. 2014[218]	RCT	200 patients with gonarthrosis	2 groups: - NSAIDs - HA	25 mg of high MW HA (2700 kDa), Chugai Pharmaceutical Co.	joint stiffness	I
Jørgensen et al. 2010[205]	RCT	337 patients with gonarthrosis	2 groups: - HA - saline solution	2 ml of sodium hyaluronate (Hyalgan, 10 mg / ml)	pain at injection site	I
Jüni et al. 2007[219]	RCT	660 patients with gonarthrosis	3 groups: - High MW crosslinked HA derived from cock's crest (Synvisc) - Medium-MW non-crosslinked HA derived from cock's crest (Orthovisc) - Low MW non cross-linked HA obtained through bacterial fermentation (Ostenil)	2 ml of Synvisc, Orthovisc and Ostenil	- joint effusion - redness at injection site - septic arthritis - anaphylactic shock	I
Lee et al. 2006[206]	RCT	146 subjects with gonarthrosis	2 groups: - High MW HA - Low MW HA	Hyruan Plus (high MW 3000 kD), Hyal (medium MW 750 kD)	- pain at injection site - localized pruritus - urticaria - myalgia - paresthesias	I
Leighton et al. 2014[207]	RCT	442 subjects with gonarthrosis	2 groups: NASHA Methylpredni-solone acetate (MPA)	60 mg/3 ml of Durolane	- pain at injection site - arthralgia - joint stiffness - joint swelling	I

To be continued

Continue from **Table XVIII.**

Lund-sgaard et al. 2008[225]	RCT	251 subjects with gonarthrosis	3 groups: - 2 ml of HA - 20 ml saline solution - 2 ml saline solution	2 ml of Hyalgan (10.3 mg/ml)	No adverse events	I
Maheu et al. 2011[208]	RCT	276 patients with gonarthrosis	2 groups: - 20 mg of medium MW HA (F60027) - 16 mg of high MW HA (Hylan G-F20)	20 mg of F60027 (Structorial) 16 mg of Hylan G-F20 (Synvisc)	pain at injection site	I
Medina et al. 2006[220]	Systematic review	7 studies (gonarthrosis)	-	Artzal, Synvisc, Hyalgan, Durolane, Suplasyn, NRD101	allergic manifestations: - sweating - pallor - feeling of thoracic or epigastric oppression - cyanotic skin - hypotension	I
Migliore et al. 2009[102]	RCT	42 subjects with coxarthrosis	2 groups: - 4 ml HA derived from bacterial fermentation - 4 ml mepivacaine 2%	4 ml of Hyalubrix (60 mg)	pain at injection site	I
Munteanu et al. 2011[140]	RCT	151 patients with osteoarthritis of first metatarso-phalangeal joint	Participants randomly allocated to receive up to 1 ml intraarticular injection of both Hylan G-F20 or placebo	Hylan G-F 20 (Synvisc)	cellulitis at injection site	I
Navarro-Sarabia et al. 2011[114]	RCT	306 subjects with gonarthrosis	2 groups: - HA - saline solution	2.5 ml (1%) of medium MW (900000 Da) sodium hyaluronate, obtained from fermentation of Streptococcus zoopidemicus (Adant)	allergic reaction not specified	I
Neustadt et al. 2005[209]	RCT multicenter	327 patients with gonarthrosis	3 groups: - 4 injections of high MW HA (O4) - 3 HA and 1 arthrocentesis (O3A1) - 4 arthrocentesis (A4)	2 ml / 30 mg of highly purified high MW HA (Orthovisc,1-2,9 MDa)	- pain at injection site - arthralgia - hematoma/ecchymosis at injection site - rhinopharyngitis - headache - vertebral pain - heart attack -gastrointestinal bleeding	I
Oliveras-Moreno et al. 2008[226]	RCT	41 subjects with pain at temporo-mandibular joint (Wilkes stage II)	2 groups: - HA - methocarbamol + paracetamol	1 ml of sodium hyaluronate 1% (Ostenil mini)	No adverse events	I
Özgen et al. 2012[78]	RCT	24 subjects with tendinitis of supraspinatus	2 groups: - HA - physical means	2 ml/16 mg of G-F 20 with a MW of 6x106	No adverse events	I
Palmieri et al. 2013[159]	RCT	62 patients with bilateral gonarthrosis	3 groups: - 66 mg of HA - 49.5 mg of HA + 5mg of diclofenac	66 mg/2 ml of HA (Variofill®)	No adverse events	I

To be continued

Continue from **Table XVIII.**

			sodium - 49.5 mg of HA + 5mg of sodium clodronate			
Petrella et al. 2015[156]	RCT multicenter	98 subjects with gonarthrosis	3 groups: - HA (Hydros) - HA + triamcinolone acetonide 10 mg (Hydros TA) - HA (Synvisc-One)	- Hydros (hydrogel with HA suspended in HA solution) - Hydros TA (HA+10 mg triamcinolone acetonide) - Synvisc-One® (hylan G-F 20)	- arthralgia - joint swelling - joint stiffness - vertebral pain - colitis - bronchopneumonia - meniscal lesion	I
Qvistgaard et al. 2006[99]	RCT	101 patients with coxarthrosis	3 groups: - 1ml/40 mg methylpredni-solone + 2 fake injections - 3 injections HA (2 ml)- 3 injections of saline solution (2 ml)	2 ml of HA (Hyalgan®)	pain at injection site	I
Reichen-bach et al. 2007[211]	Systematic review	13 studies (gonarthrosis)		Artzal, Orthovisc, Hyalgan, Ostenil, Bio-Hy	- pain at injection site - joint swelling	I
Richette et al. 2009[101]	RCT	122 patients with symptomatic coxarthrosis	2 groups: - HA - saline solution	2.5 ml of HA (Adant) obtained from Streptococcus fermentation with average MW 900000 Da	- pain at injection site - hematoma at injection site - pruritus	I
Saito et al. 2009[212]	Systematic review	5 studies (knee rheumatoid arthritis)		Not specified	pain at injection site	I
Saito et al. 2010[191]	Systematic review	19 studies (chronic shoulder pain)		NRD 101, Artz (900 kD), SLM-10 (1900 kD), Hyalart, Subenyl (1900 kD), Orthovisc (1000-2900 kD), Hyalgan (500-730 kD)	- pain at injection site - joint swelling	I
Shi et al. 2003[190]	Cochrane review	11 studies (temporo-mandibular joint disorders)			- discomfort at injection site - joint swelling	I
Stahl et al. 2005[139]	RCT	52 patients with grade II rhizoartrosis	2 groups: - methyl-prednisolone acetate - HA	15 mg of sodium hyaluronate (Ortho-Visc)	No adverse events	I
Strand et al. 2012[227]	RCT	379 patients with gonarthrosis	2 groups: - HA - PBS	30 mg/3 ml crosslinked HA (Gel-200)	No adverse events	I
Tang 2012[221]	RCT	162 patients with knee Kashin-Beck disease	2 groups: - Intra-articular HA - meloxicam per os	25 mg of HA (10 g/ml, > 800 kDa)	local reactions at injection site	I
Tikiz et al. 2005[98]	RCT	43 patients with coxarthrosis	2 groups: - Low MW HA - High MW HA	- Low MW HA (Ostenil, 1,2-1,4x106 Da; 1%) - High MW HA(hylan G-F 20, Synvisc, 7x106Da)	- pain at injection site - joint swelling	I

To be continued

Continue from **Table XVIII.**

Waddell et al. 2007[107]	Systematic review	(gonarthrosis)		Synvisc (hylan G-F 20), Hyalgan (sodium hyaluronate), Supartz (sodium hyaluronate), Orthovisc (high MW HA) and Euflexxa (1% sodium hyaluronate)	- pain at injection site - joint swelling	I
Wang et al. 2004[213]	Systematic review	20 studies (gonarthrosis)		Cross-linked HA (Synvisc), non-cross-linked HA (Hyalgan, Orthovisc, Artz) and bio-engineered HA	- pain at injection site - joint swelling - vasculitis - hypersensitivity reactions	I
Wobig et al. 1998[217]	RCT	110 patients with gonarthrosis	2 groups: - HA - saline solution	2 ml of hylan G-F 20	- muscle cramps - hemorrhoids - impatience	I
Wobig et al. 1999[214]	RCT	70 patients with gonarthrosis	2 groups: - High MW HA - Low MW HA	- High MW HA (hylan G-F 20, 0.8%) - Low MW HA (1%)	- pain at injection site - joint swelling - intraarticular effusion	I
Yu et al. 2014[215]	Systematic review	7 studies (gonartrosis in KBD)	-	-	- pain at injection site - joint swelling - intraarticular effusion -bleeding at injection site	I

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