TECHNOLOGY REVIEW (MINI-HTA)

HYALURONIC ACID INJECTION FOR VARIOUS JOINT DISORDERS

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

Background

The substantial impact of joint disorders on individuals' daily lives and the significant burden they impose on healthcare systems globally are undeniable. Joints play a vital role in facilitating movement, and chronic pain conditions affecting those present significant challenges in treatment and rehabilitation. The International Classification of Diseases (ICD-11) defines chronic pain as pain persisting beyond three months, with prevalence rates ranging from 11% to 40%. Musculoskeletal conditions, including back pain, musculoskeletal disorders, and neck pain, are major contributors to this burden. According to Global Burden of Disease (GBD) 2019 data, approximately 1.71 billion people globally live with musculoskeletal conditions. Osteoarthritis affected about 528 million people worldwide in 2019, marking an increase of 113% since 1990. This condition commonly affects joints such as the knees, hips, spine and small joints in the hands, impacting the surrounding muscles and tissues.

While conservative management strategies are often recommended, hyaluronic acid (HA) injections have emerged as potential intervention to alleviate symptoms across various joints. Hyaluronic acid has been explored as adjunct therapies, particularly in cases where conservative approaches are indicated. Although evidence suggests potential benefits, cautious interpretation is warranted due to variations in treatment response and the need for skilled administration by healthcare practitioners. This technology review focuses on five joint disorders affecting the spine, shoulder, hip, knee, and ankle. Recognising the widespread use of HA injections and the increase number of private practice clinicians offering this treatment for various joint disorders, the Director of Medical Practice Division, Ministry of Health Malaysia (MOH), requested this technology review to evaluate the effectiveness and safety of hyaluronic acid injections.

Objective/ aim

The objective of this technology review is to assess the effectiveness, safety and economic implications of hyaluronic acid injection in the treatment of joint disorders affecting the spine, shoulder, hip, knee, and ankle among the adult population.

Results and conclusion:

Search results

The initial searches yield a total of **10,284** records. Among these, **2,554** titles were screened using predefined inclusion and exclusion criteria. After applying eligibility criteria, **44** full text articles were selected for review. These comprised four systematic reviews with network meta-analysis, 12 systematic review with meta-analysis, seven systematic reviews, 12 RCTs, one non-RCT, three prospective single-arm clinical trials, one health technology assessment, and

four before-after studies. The studies were predominantly conducted across various countries spanning four continents -

- ASIA: China (6), Taiwan (3), Japan (3), Korea (2), Iran (2), Turkey (1), Pakistan (1), Iraq (1), India (1), Israel (1)
- EUROPE: Italy (7), Belgium (3), Netherlands (2), United Kingdom (1), Spain (1)
- NORTH AMERICA: Canada (1), the United States (4),
- SOUTH AMERICA: Brazil (3)

Effectiveness

(a) Disorders of the spine, shoulder, hip, knee and ankle

	Disorders	Outcomes of hyaluronic acid treatment
i.	Spine: • Lumbar spinal stenosis	No statistical significant differences in pain improvement and functional outcomes between the hyaluronic acid-carboxymethylcellulose (HA-CMC) group and the CS group.
	• Lumbar radiculopathy	HA-CMC injection showed statistical pain improvement at 2 weeks post-SNRB. However, at 6 and 12 weeks, HA-CMC showed similar effects with corticosteroid injection.
ii.	Shoulder • Rotator cuff tears • Adhesive shoulder capsulitis • Rotator cuff tendinopathy • Supraspinatus tendinitis and tendinosis	HA injection alone did not demonstrate superiority over placebo or other non-surgical therapies. HA injection provided only short-term pain relief and increased range of motion (ROM) without functional recovery. In the long-term, no significant impact on pain, ROM, and functional recovery.
iii.	Knee • Knee/patellar tendinopathy • Knee/patellar chondropathy • Knee patellofemoral syndrome • Knee meniscus/ligament	HA injection alone or in combination with physical therapy provided effective pain relief and enhanced functionality over both short and long-term durations. HA injection do not benefit for knee meniscus/ligament injury.
iv.	Ankle tendinopathies	In the short-term, both HMW-HA and LMW-HA injections demonstrated potential for pain reduction, with HMW-HA injection showed statistically significance in treating plantar fasciopathy.

		For patients with Achilles tendinopathy, HA injection reduced pain and improved functionality in both short-term and long-term durations.
v.	Hip-related conditions	There is currently no retrievable evidence demonstrating the effectiveness of HA injection treatment for hip-related conditions.

(b) Osteoarthritis of the shoulder, hip, knee and ankle

	Disorders	**Outcomes of hyaluronic acid treatment**
i.	Shoulder OA	IAHA may offer short-term relief, especially when combined with physical therapy. These benefits in pain relief and shoulder function may sustained over the long-term for patients with mild to moderate shoulder OA.
ii.	Hip OA	Despite mixed findings, the majority of studies indicate that IAHA did not yield significant improvements in pain and hip function over the short-term duration. However, for long-term hip survivorship, PRP was shown to be superior to IAHA.
iii.	Knee OA	HA treatments provided good short-term relief but lacked the long-term effectiveness offered by PRP injections. PRP injections when used as comparator demonstrated superiority over IAHA, sustaining pain relief, functional improvement, and reduction in stiffness in both short-term and long-term durations.
iv.	Ankle OA	IAHA does not provide significant difference in pain relief and functional improvement for ankle OA.

There was substantial evidence retrieved on the effectiveness of hyaluronic acid injection in the treatment of joint disorders affecting the spine, shoulder, hip, knee, and ankle among the adult population. The existing evidence supports the effectiveness of HA injections in reducing pain, improving functionality, increasing range of motion, and enhancing quality of life, particularly when integrated with rehabilitative treatment in certain disorders. It should be noted, however, that these benefits were short-term (less than six months) and did not persist over the long-term (beyond six months) after the intervention. There is inadequate strong evidence available to establish HA superiority over other treatments such as corticosteroids, physiotherapy or other conservative management.

Safety

Hyaluronic acid injection has shown to be a generally well-tolerated intervention for various joints disorders, including those affecting the shoulder, hip, knee, and ankle, with minimal occurrence of serious adverse events. Across all joints, local responses such as swelling, pain at injection site, musculoskeletal pain, joint pain, joint stiffness, pain flare ups, local skin reactions, pruritis, oedema, and effusion were frequently reported, mostly of mild and temporary nature. Specifically regarding glenohumeral osteoarthritis, a comprehensive systematic review reported a pooled adverse event rate of 33.92%, with documented serious adverse events, including severe musculoskeletal pain, abscess, chest pain, and occurrences of cancer.[45] Another study reported the treatment-emergent adverse events (TEAE) incidence of 49.3% in the IA DF-HA group, with no severe TEAEs observed. However, these events were of moderate severity, showed improvement during the study, and were not attributed to the study drug.[46] These findings highlight the importance of carefully considering the specific HA formulation and patient characteristics when administering HA treatments.

Organisational

The length of follow-up varied among studies, distinguishing between short-term (< 6 months) and long-term (≥ 6 months) effects. Patient satisfaction was addressed in a limited number of studies, showed the highest levels of satisfaction among individuals who received HA at 12 weeks post-injection. The HA procedure is administered in outpatient settings and performed by skilled and experienced practitioners, primarily utilising image-guided techniques. Moreover, the registration of hyaluronic acid injection with the Medical Device Authority indicates adherence to regulatory standards for safety and quality assurance in Malaysia.

Recommendations regarding HA treatments vary across guidelines, with evidence suggesting that HA injections offer limited or no benefit for conditions such as rotator cuff tears, glenohumeral joint osteoarthritis, and osteoarthritis of the hip and knee. Corticosteroid injections emerge as a commonly recommended treatment option for shoulder pain and osteoarthritis of the hip and knee.

Economic implication

Malik AT et al. (2020) analysed the United States national insurance claims data, which revealed significant differences in pre-operative elective arthroscopic rotator cuff repair costs between Medicare Advantage (MA) and commercial insurance beneficiaries, with MRI scans and office visits being the major cost drivers. Moreover, per-patient average reimbursements varied across different resources, with hyaluronic acid injections reimbursement rate of $422 for MA and $602 for commercial insurance. Hence, highlighting the financial burden faced by both patients and insurers.

Conclusion

In summary, HA injections are effective in reducing pain, improving functionality, increasing range of motion, and enhancing quality of life, for conditions such as rotator cuff tears and

adhesive shoulder capsulitis, knee disorders associated with tendinopathies and chondral injuries, ankle tendinopathies, and mild to moderate glenohumeral osteoarthritis, especially when combined with rehabilitation. However, these benefits are short-term, lasting less than six months, and are not sustained long-term (beyond six months) post-intervention. Compared to alternatives like PRP, HA injection is less effective in the long-term. Evidence for HA injection in rotator cuff tendinopathy is limited and inconsistent, indicating the need for further robust trials to determine optimal use and long-term benefits.

Hyaluronic acid-carboxymethylcellulose (HA-CMC) shows potential as an alternative to corticosteroids in selective nerve root block (SNRB) for spinal stenosis and lumbar radiculopathy. However, the benefits are minimal due to limited studies and small sample sizes, requiring further high-quality research before recommending its use.

For knee OA, HA treatments provide good short-term relief but lack the long-term effectiveness offered by PRP injections comparatively.

Hyaluronic acid injection yields no effectiveness for conditions of knee meniscus or ligament injury, hip osteoarthritis, and ankle osteoarthritis. Throughout the literature reviewed, there is inadequate strong evidence available to establish the superiority of HA over other treatments such as corticosteroids, physiotherapy, or other conservative management approaches. Further high-quality research is needed to determine the long-term benefits and to guide clinical practice.

Recommendations regarding HA treatments vary across guidelines, with evidence suggesting limited or no benefit for conditions such as rotator cuff tears, glenohumeral joint osteoarthritis, and osteoarthritis of the hip and knee. Hyaluronic acid injections are generally well-tolerated, with minimal incidence of serious adverse events. However, caution should be exercised in cases of glenohumeral osteoarthritis due to the potential risk of severe musculoskeletal pain, abscess formation, chest pain, and occurrences of malignancy. Given the diverse injection techniques required for different pathological conditions, it is advisable that these injection to be performed by practitioners with specialised skills and extensive experience.

Methods

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® ALL 1946 to October 6, 2023, EBM Reviews - Cochrane Central Register of Controlled Trials September 2023, EBM Reviews - Database of Abstracts of Reviews of Effects - 1st Quarter 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to November 1, 2023, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016. Searches were also run in Pubmed, US FDA and INAHTA websites. Google was used to search for additional web-based materials and information. The search was limited to articles on human. There was no language limitation in the search. Additional articles were identified from reviewing the references of retrieved articles. The last search was conducted on 8th November 2023.

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ABBREVIATION	
ACL	Anterior cruciate ligament
CASP	Critical Appraisal Skills Programme
ESWT	Extracorporeal shockwave therapy
FADI	Foot and Ankle Disability Index
HA	Hyaluronic acid
HA-CMC	Hyaluronic acid-carboxymethylcellulose
IA	Intra-articular
LLRP	Lower leg radiating pain
SNRB	Selective nerve root block
LANSS	Leeds assessment of neuropathic symptoms and signs
MD	Mean difference
MRI	Magnetic resonance imaging
NRS	Numerical rating scale
ODI	Oswestry Disability Index
PRP	Platelet-rich plasma
RCT	Randomised controlled trial
RD	Risk difference
RR	Risk ratio
SD	Standard deviation
SH	Sodium hyaluronate
RMDQ	Roland Morris Disability Questionnaire
SF-36	Short Form questionnaire – 36 items
PCS	Physical component scores
MCS	Mental component scores
VAS	Visual analogue scales
VISA-A	Victorian Institute of Sport Assessment-Achilles
VISA-P	Victorian Institute of Sport Assessment-Patella
WOMAC	Western Ontario and McMaster Universities Arthritis Index
95% CI	95% Confidence interval

1.0 BACKGROUND

Joints serve as the points where two or more bones meet, encompassing surrounding soft tissues, such as cartilage, tendons and ligaments. Cartilage is the hard slippery flexible tissue covering the ends of bones at a joint and facilitates smooth movement. Tendons are sturdy and flexible bands, connect muscles to bones in enabling joint mobility. While ligaments, linking joint bones and provide stability during movement. Various joints in the body, including the shoulder, elbows, hips, knees, ankle, knuckles, and the spine, contribute to overall joint function. Joint disorders comprising diseases or injuries, are often associated with pain, impacting joint functionality and restricting basic tasks.[1] Joint pain may occur from diverse injuries or conditions, potentially linked to arthritis, bursitis, or muscle-related discomfort.[2] This discomfort not only affects joint function but also limit individuals in performing everyday activities. Severe joint pain presents a significant challenge to one's quality of life, leading to healthcare-seeking behaviour and contributing to disability.[3]

The International Classification of Diseases (ICD-11) defines chronic pain as pain persisting beyond three months, with prevalence rates ranging from 11% to 40%.[3] Chronic pain conditions, such as back pan, musculoskeletal disorders, and neck pain, are major contributors.[3] Musculoskeletal conditions comprising muscles, bones, joints, and connective tissues, also top the global need for rehabilitation. According to Global Burden of Disease (GBD) 2019 data, approximately 1.71 billion people globally live with musculoskeletal conditions.[4]

Osteoarthritis (OA) is one of the significant contributors to disability among musculoskeletal conditions, affected about 528 million people worldwide in 2019, and an increase of 113% since 1990. While more prevalent in older people (about 70% are older than 55), osteoarthritis can also impact younger populations, including athletes and those with joint injuries. About 60% of affected individuals are women.[5] The condition commonly affects the knees, hips, spine and small joints in the hands, impacting the surrounding muscles and tissues.

Treatment for these conditions focuses on relieving symptoms, improving joint function, and encouraging a return to daily activities. Conservative management including rehabilitation and medications is initially recommended. As an adjunct therapy, various injection options are available in clinical practice as symptomatic treatments. If conservative approaches ineffective, surgical intervention becomes a viable option.

Hyaluronic acid (HA) is a major component of synovial fluid and cartilage, plays a crucial role in joint health. Exogenous administration of HA aims to supplement the viscoelasticity of synovial fluid, lubricate joint surfaces, inhibit inflammation and nociception, and promote tissue healing. Intra-articular (IA) HA injections have been used for over 30 years for knee osteoarthritis. More recently, HA injections have been used for tendonitis and tendinopathies

around other joints, including the shoulder, elbow and ankle. Injection of IAHA may be difficult in a non-swollen joint and is not intended for flares with joint swelling.[6]

This technology review focuses on five joint disorders affecting the spine, shoulder, hip, knee, and ankle.

SPINE

Low back pain is a leading cause of years lived with disability (YLDs). Based on the GBD Study 2021, low back pain affected 619 million people globally in 2020, with a projected increase to 843 million by 2050.[7] The incidence varies from 5% to over 30%, with a lifetime prevalence of 60% to 90%.[8] Lumbosacral radiculopathy caused by nerve compression in the lower back, is a common neurological complaint. Symptoms include radiating pain, numbness, weakness, and loss of reflexes.[8] Initially, conservative approaches such as patient education (e.g. participating in weight loss programme), physical therapy (such as engaging in McKenzie exercises), and medications are recommended, with the aim to prevent further damage. Interventional techniques like steroid injections provide long-term relief, and surgery may be considered in refractory cases.[9]

SHOULDER

Shoulder disease is a major cause of musculoskeletal disability, with a global prevalence of shoulder pain ranging from 0.67% to 55.2%.[10, 11] Women generally experience higher rates than men, and the rates are also higher in those of high-income nations. The incidence of shoulder pain varies from 7.7 to 62 per 1,000 persons per year (median 37.8 per 1,000 persons per year),[10] with rotator cuff pathology being the leading cause of shoulder-related disability.[12] In individuals over 50 years, rotator cuff injuries occur approximately in 25% of cases, resulting in 200,000 to 300,000 new cases worldwide each year.[13] Types of rotator cuff injuries are illustrated in Figure 1 and severity ranges from inflammation to complete tendon tears.

Rotator cuff injuries predominantly affect the supraspinatus muscle, causing symptoms such as joint stiffness, instability, and sharp pain during specific movements. Surgical intervention is the gold standard of treatment. But in selected cases the conservative treatment is recommended and several authors suggest the use of intra-articular infiltrations of hyaluronic acid.[14]

Frozen shoulder, or adhesive capsulitis, affects 2-5% of the population with higher in females and the elderly. This disorder limits both active and passive shoulder motion, particularly in abduction and external rotation, accompanied with severe pain at night. Treatment focuses on pain relief and restoring shoulder function, and the condition is considered self-limiting within 1-3 years.[15] Adhesive capsulitis occurs between 40 to 60 years, and is associated with various diseases and medical history, including diabetes, thyroid dysfunction, autoimmune diseases, breast cancer treatment, stroke, or myocardial infarction.[16]

Rotator cuff tendinopathy is a chronic, degenerative or overuse, non-inflammatory disorder and usually healed within two to six months, commonly managed with exercise therapy. Shoulder tendonitis involves inflammation of the tendon and resolves within days to weeks. In addition to exercise therapy, various injection options serve as symptomatic treatments.[17]

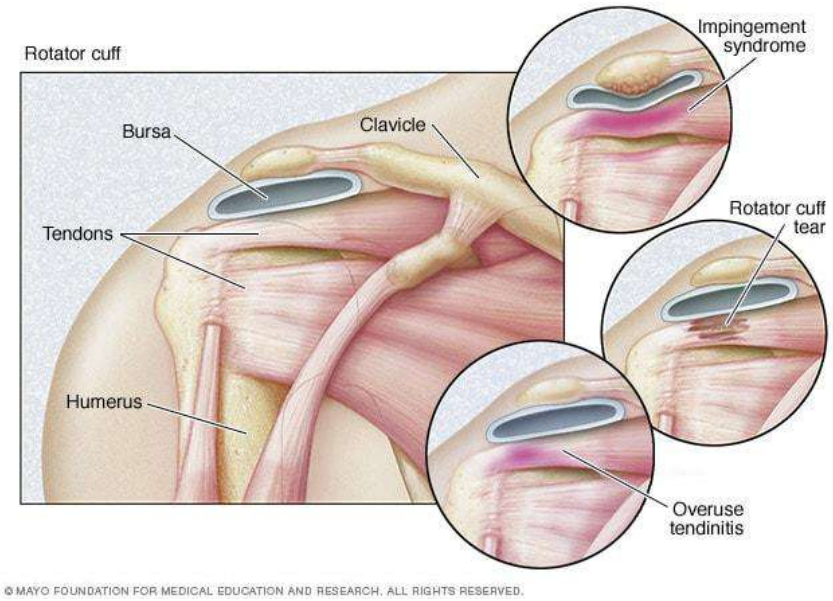

Figure1: Types of rotator cuff injuries
(Source: https://www.mayoclinic.org/diseases-conditions/rotator-cuff-injury/symptoms-causes/syc-20350225)

KNEE AND ANKLE DISORDERS

A spectrum of non-osteoarthritic conditions affecting the knee, and ankle joints presents unique challenges and therapeutic considerations. While IAHA injections have primarily been investigated in the context of OA management, emerging evidence suggests their potential utility in addressing symptoms associated with these diverse pathologies.

In the realm of knee pathology, various non-osteoarthritic pathologies, such as meniscal tears, ligamentous injuries, and patellofemoral disorders, present significant sources of pain and functional impairment. Meniscal tears, characterised by disruptions in the fibrocartilaginous menisci, result in joint instability, swelling, and mechanical symptoms. Ligamentous injuries, including anterior cruciate ligament (ACL) tears, compromise knee joint stability and predispose individuals to recurrent episodes of instability and cartilage damage. Patellofemoral disorders encompass a spectrum of conditions affecting the articulation between the patella and femur, ranging from patellar maltracking to chondromalacia patellae, contributing to anterior knee pain and functional limitations. While IAHA injections have predominantly been explored in the context of knee OA, their potential role in providing symptomatic relief and augmenting joint function in non-osteoarthritic knee pathologies warrants further investigation.

Similarly, in the ankle joint, non-osteoarthritic conditions such as ligamentous injuries, tendinopathies, and osteochondral lesions present significant clinical challenges. Ankle ligamentous injuries, including sprains and tears of the lateral or medial ligament complexes,

lead to joint instability, recurrent swelling, and functional impairment. Tendinopathies, such as Achilles tendinopathy or peroneal tendinopathy, result in tendon degeneration, pain, and reduced ankle mobility. Osteochondral lesions, involving damage to the articular cartilage and underlying bone, predispose individuals to chronic pain, swelling, and mechanical symptoms. While IAHA injections have primarily been investigated in the context of ankle OA, their potential efficacy in addressing symptoms associated with non-osteoarthritic ankle pathologies warrants exploration.

OSTEOARTHRITIS

Osteoarthritis stands as a significant public health challenge globally, characterised by joint pain, stiffness, and functional limitations. Despite its prevalence, accurately quantifying the incidence and prevalence of OA remains elusive due to the discordance between clinical symptoms and structural changes in affected joints. Technological advancements in imaging, notably magnetic resonance imaging (MRI), have enhanced our understanding of OA's structural abnormalities beyond conventional radiographic assessments. The aging demographic landscape, coupled with escalating rates of risk factors such as obesity and sedentary lifestyles, underpins the rising burden of OA across diverse populations.

Among the joints commonly afflicted by OA, the hip, knee, and ankle represent focal points of clinical attention due to their substantial impact on mobility, pain, and quality of life. Hip OA, in particular, poses a formidable healthcare challenge globally, accentuated by its association with diminished work productivity, increased healthcare utilisation, and the potential need for invasive interventions like total hip arthroplasty. Knee OA emerges as the most prevalent form of arthritis, exhibiting an upward trajectory in incidence parallel to escalating life expectancies and obesity rates. Despite the high prevalence of radiographic findings, not all individuals with knee OA experience symptomatic manifestations, underscoring the complexity of its clinical presentation. Ankle OA, though less prevalent than its knee and hip counterparts, exerts comparable disability and functional limitations, impeding daily activities and diminishing overall quality of life.

In light of the multifaceted impact of OA on affected individuals and healthcare systems, exploring efficacious therapeutic modalities is imperative. Intra-articular hyaluronic acid injections have garnered attention as a potential intervention to alleviate symptoms associated with OA across various joints. Hyaluronic acid, a naturally occurring component of synovial fluid, aims to restore joint lubrication and mitigate inflammation, thereby offering a promising avenue for OA management.

Given the widespread use of IAHA injections and the growing number of private practice clinicians offering this treatment for various joint disorders, the Director of Medical Practice Division, Ministry of Health Malaysia (MOH), requested this technology review to evaluate the effectiveness and safety of IAHA injection

2.0 OBJECTIVE / AIM

The objective of this technology review is to assess the effectiveness, safety and economic implications of intra-articular hyaluronic acid injection in the treatment of joint disorders affecting the spine, shoulder, hip, knee, and ankle among the adult population.

3.0 TECHNICAL FEATURES

Hyaluronic acid was initially isolated from the vitreous body of the bovine eye in 1934 by Karl Meyer and John Palmer,[18] and gained attention for its physico-chemical properties. Meyer and Weissmann described its chemical structure in 1954, and pharmaceutical-grade HA was produced in 1979 by Balazs. Since the early 1980s, HA has been a main component in intraocular lenses due to its safety and protective effect on the corneal endothelium. Additionally, it has also shown benefits in treating joint and skin diseases, wound healing, and soft tissue augmentation.[19]

This long polysaccharide composed of repeating disaccharides, with a molecular weight (MW) up to 2×10^7 daltons (Da).[18] Hyaluronic acid plays a crucial role in various processes, including cell signalling, tissue regeneration, and wound repair. With unique properties (such as biocompatibility, biodegradability, and viscoelasticity), exogenous HA has been explored in drug delivery systems and treatments across medical fields, including cancer, ophthalmology, arthrology, pneumology, rhinology, urology, aesthetic medicine and cosmetics (Figure 2).[19]

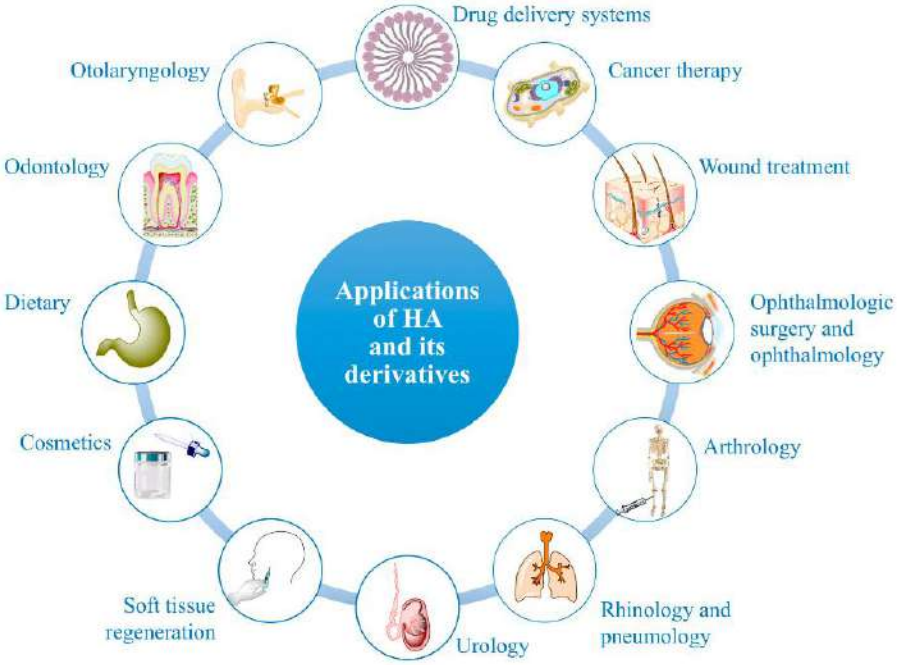

Figure 2: Medical, pharmaceutical, cosmetic and dietary applications of hyaluronic acid and its derivatives[19]

Action of intra-articular hyaluronic acid injection

In the context of IAHA injection, HA serves as a major component in both cartilage and synovial fluid. The aim of these injections is to restore mechanical properties and elicit various biological effects, including anti-inflammatory action, reduced enzyme production, anti-oxidant effects, anabolising impact on cartilage, and direct analgesia.[6] Injected HA effectively suppresses cytokine-induced responses, reduced synovial inflammation, relieves pain, and subsequently enhances joint function.[16]

Hyaluronic acid products are derived from rooster combs or bacterial fermentation and stabilised for injection. Several HA products are available including sodium hyaluronate (Hyalgan, Adant) and cross-linked HA (Synvisc, Monovisc). The injections are administered in the clinic as a course of two to five, usually one week apart.

4.0 METHODS

A systematic review was conducted. Review protocol and search strategy was developed by the main author and an *Information Specialist*.

4.1 SEARCHING

Electronic databases searched through the Ovid interface:

- Ovid MEDLINE® ALL 1946 to October 6, 2023
- EBM Reviews - Cochrane Central Register of Controlled Trials September 2023
- EBM Reviews - Database of Abstracts of Reviews of Effects - 1st Quarter 2016
- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to November 1, 2023
- EBM Reviews - Health Technology Assessment 4th Quarter 2016
- EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016

Other databases:

- PubMed
- Other websites: US FDA, INAHTA

General databases such as Google were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 2** showed the detailed search strategies. The last search was conducted on 8th November 2023.

4.2 SELECTION

Two reviewers (AA and KI) independently screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised using *the ROBIS tool, the Cochrane Risk of Bias (RoB 2.0),* and *the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group (non-RCT) checklists*. Studies were graded according to *US/Canadian Preventive Services Task Force* (**Appendix 1**). Data were extracted and summarised in evidence table (AH and MA) as in **Appendix 3**. Disagreement was resolved by discussion. No meta-analysis was conducted for this review. The inclusion and exclusion criteria were:

Inclusion criteria

a.	**Population**	Adult patient with (i) Spine • Osteoarthritis • Spondylosis • Spondylolisthesis • Spinal stenosis • Prolapse intervertebral discs / herniated discs • Radiculopathy (ii) Shoulder • Osteoarthritis • Tendonitis • Rotator cuff tear • Adhesive capsulitis (iii) Hip • Osteoarthritis • Tendonitis • Ligament / tendon injury • Avascular necrosis • Joint contractures (iv) Ankle • Osteoarthritis • Tendonitis • Ligament / tendon injury (v) Knee • Tendonitis • Ligament / tendon injury • Articular cartilage (chondral) injury • Meniscus injury • Patellofemoral syndrome • Joint contractures

		• Muscle spasm
b.	**Interventions**	Hyaluronic acid injection
c.	**Comparators**	Standard care, placebo, no treatment, corticosteroid, platelet-rich plasma (PRP), botulinum toxin Type A (BoNT-A), physiotherapy, exercise therapy
d.	**Outcomes**	Effectiveness: i. Pain relief ii. Functional improvement iii. Efficacy kinetics iv. Quality of life Safety: i. Side effects / adverse events ii. Complications iii. Mortality Organisational issues: i. Length of follow up ii. Patients satisfaction Economic implications: i. Cost-effectiveness / cost-utility / cost-analysis
e.	**Study design**	Health Technology Assessment (HTA) reports, systematic review (SR) with/out meta-analysis, randomised controlled trial (RCT), non-RCT, case control study, cohort, pre- and post-intervention study, cross sectional.
f.	Full text articles published in English	

Exclusion criteria

a.	**Interventions**	Other modes of delivering hyaluronic acid, aside from injection.
b.	**Study design**	Case series, case report, survey, anecdotal, animal study, laboratory study, narrative review
c.	Non-English full text articles	

This report present finding concerning five major joints – i.e.: the spine, shoulder, hip, knee and ankle joints – each associated with distinct conditions. The effectiveness results are divided into three parts: Part I covers joint disorders affecting the spine and shoulder; Part II addresses joint disorders affecting the hip, knee and ankle; and Part III focuses on osteoarthritis of the shoulder, hip, knee and ankle.

PART I : JOINT DISORDERS AFFECTING THE SPINE AND SHOULDER

5.0 RESULTS

Search results

(a) Spinal disorders

A systematic search was conducted to assess the utilisation of HA for various spinal conditions, including spondylosis, spondylolisthesis, spinal stenosis, prolapsed intervertebral discs or herniated discs, radiculopathy, and osteoarthritis. However, no pertinent evidence was retrieved for spinal spondylosis, spondylolisthesis, prolapsed intervertebral discs or herniated discs, and osteoarthritis. For spinal osteoarthritis, spinal spondylosis, spinal spondylolisthesis, and prolapsed intervertebral discs, a total of **34, 184, 183, and 222** records were respectively identified through the Ovid interface and PubMed databases. Titles were screened using the inclusion and exclusion criteria and none met the criteria. In spinal stenosis, **14** records were identified, **4** duplicates were removed, and **10** potentially relevant titles were screened. **One** abstract was potentially relevant. Similarly, for spinal radiculopathy, **184** records were identified, from which **two** potentially relevant titles were screened, resulting in obtaining the full text of one abstract considered potentially relevant. After conducting a comprehensive review and assessment of the inclusion and exclusion criteria, **two** full-text articles were included into our analysis. These articles consisted of one RCT each for spinal stenosis and spinal radiculopathy; both studies were conducted in Korea.

(b) Shoulder disorders

A comprehensive search was conducted across Ovid interface and PubMed databases for rotator cuff tears, adhesive shoulder capsulitis, and rotator cuff tendinopathy.

For rotator cuff tears, **92** records were identified. Following the removal of **23** duplicates, **69** potentially relevant titles underwent screening based on predefined inclusion and exclusion criteria, **12** abstracts were considered potentially relevant, resulting in the inclusion of **four** full-text articles. These articles consisted one systematic review with network meta-analysis, one systematic review, and two prospective single-arm clinical trials, primarily conducted in Italy, Belgium and China. **Eight** records were excluded for various reasons: four were already incorporated into systematic reviews, one were found to have irrelevant interventions, two did not align with the intended population, and one was published over 20 years ago.

The search in adhesive shoulder capsulitis yielded **117** records, of which **14** duplicates were eliminated, leaving **103** potentially relevant titles for screening based on the predefined criteria. From these, **16** abstracts were selected for full-text retrieval, resulting in the inclusion of **three** full-text articles, comprising one meta-analysis of RCTs, one systematic review, and one health technology assessment. The studies were conducted in Italy, China, and the United Kingdom. **Thirteen** records were excluded for various reasons: 10 had already been included in systematic reviews, one were found to have irrelevant interventions, one did not match the intended population, and one was unable to retrieve the full text article.

Additionally, rotator cuff tendinopathy search identified **95** records, with **10** duplicates removed, resulting in **85** potentially relevant titles were screened using the predefined inclusion and exclusion criteria. Of these, **13** abstracts were selected for full-text retrieval, leading to the inclusion of **six** full-text articles into our analysis. These comprised one systematic review with network meta-analysis, three RCTs, one non-RCT, and one prospective single-arm clinical trials, mainly conducted in Italy, Iran, Taiwan, and Turkey. **Seven** records were excluded for various reasons: three had already been included in systematic review, one was found to have irrelevant interventions, and three did not match the intended population.

Overall, **15** full-text articles were included, comprised two systematic review with network meta-analysis, one meta-analysis of RCTs, two systematic reviews, five RCTs, one non-RCT, three prospective single-arm clinical trials, and one health technology assessment. The studies were conducted mainly in Italy (five studies), Iran (two studies), China (two studies), Taiwan, the United Kingdom, Belgium, and Turkey. An overview of the search is illustrated in **Figure 3**.

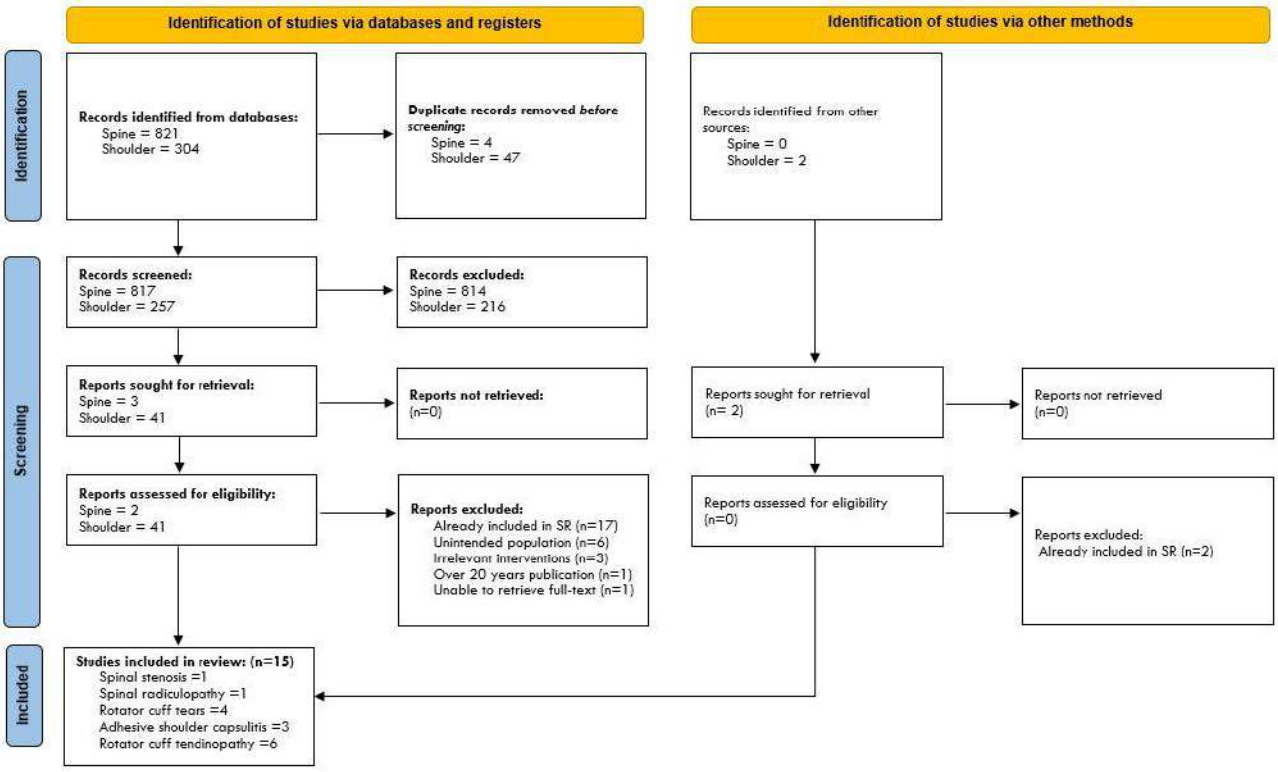

Figure 3: PRISMA 2020 flow diagram of retrieval of articles used in the results for joint disorders affecting the spine and shoulder

Quality assessment of the studies

The risk of bias in the included studies was assessed using the domain-based evaluation. Tools that are being used to assess the risk of bias are adapted from the ROBIS, Cochrane Risk of Bias (RoB 2.0), and the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group checklists. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

x	High
-	Unclear
+	Low
?	No information

Although majority of studies in the systematic review were rated as “low-risk”, there were instances of high risk coupled with low quality assessments. The risk of bias was high in both the RCT and the before-after studies. Additionally, the majority of the individual sample sizes of the trials identified and evaluated in this technology were small, potentially limiting their ability to accurately represent the broader population of interest. The results of risk of bias for the included studies are summarised in Figure 3.1 to 3.3.

Risk of bias assessment for included systematic review and meta-analysis

			Risk of bias				
			D1	D2	D3	D4	Conclusion
Study	Shoulder	Jiang X et al.[20]	+	+	+	+	+
		Osti L et al.[21]	+	+	x	x	x
		Mao B et al.[15]	+	+	+	+	+
		Papalia R et al.[22]	+	+	x	x	x
		Maund E et al.[23]	+	+	+	+	+
		Lin MT et al.[17]	+	+	+	+	+

D1: Concerns regarding specification of study eligibility criteria.
D2: Concerns regarding methods used to identify and/or select studies.
D3: Concerns regarding methods used to collect data and appraise studies.
D4: Concerns regarding the synthesis and findings.
CONCLUSION: Risk of bias in the review.

Judgement

x	High
-	Unclear
+	Low
?	No information

Figure 3.1: Risk of bias assessment for systematic review using ROBIS

Risk of bias assessment for included RCT

			Risk of bias					
			D1	D2	D3	D4	D5	Overall
Study	Spine	Ko S et al.[24]	+	+	+	+	+	+
		Ko S et al.[25]	+	+	+	+	+	+
	Shoulder	Rezasoltani Z et al.[26]	x	-	+	x	+	x
		Mohebbi R et al.[27]	+	+	+	+	+	+
		Merolla G et al.[28]	x	-	+	x	+	x
		Özgen M et al.[29]	x	-	+	x	+	x
		Meloni F et al.[30]	x	x	+	x	-	x

D1: Bias arising from the randomisation process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement

x	High
-	Some concerns
+	Low

Figure 3.2: Risk of bias assessment for RCT using RoB 2.0

Risk of bias assessment for included pre-post studies with no control

			Risk of bias											
			D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	Overall
Study	Shoulder	Tack P et al.[31]	+	+	+	-	-	+	-	-	x	+	+	-	x
		Costantino C et al.[32]	+	+	+	-	-	+	+	-	+	+	+	+	-

D1: Objective clearly stated
D2: Eligibility criteria clearly described
D3: Participants representative
D4: All eligible participants were enrolled
D5: Sample size sufficiently large to provide confidence in findings
D6: Intervention described clearly
D7: Pre-specified, valid and reliable outcome measures
D8: Blinded assessors
D9: Loss to follow-up after baseline 20% or less? Accounted for loss of follow up
D10: Statistical method for pre/post changes
D11: Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?
D12: If intervention conducted at group level, did statistical analysis take into account of individual level data to determine effects at group level?

Judgement

x	High
-	Unclear
+	Low

Figure 3.3: Assessment of risk of bias of pre-post studies with no control (NIH)

(a) Spine

Spinal stenosis

Ko S et al. (2021) was rated as low risk of bias. Study participants were randomised using random numbers generated by the RANDBETWEEN function of Microsoft Excel version 14.0 for Windows (Excel, Microsoft). Participants were assigned into an even and odd number in order at a ratio of 1:1. Those who received an even number were assigned to Group A (control group) and those with odd number were assigned to Group B (intervention group). All study investigators, hospital staff, and patients were blinded on treatment allocation information. Assessments at 2, 6, and 12 weeks after selective nerve root block (SNRB) were performed by a trained nurse who was unaware of the conduction of this study. Participants received respective intervention and all assessments were done at similar time for both groups. An intention-to-treat analysis was conducted and there were four participants loss to follow-up (9%) among the 44 participants. Outcomes were analysed and selective reporting was considered to have low risk of bias as all pre-specified outcomes were reported and analysed.[24]

Spine radiculopathy

Overall, the study by Ko S et al. (2018) had low bias risk. However, since the first author received funding from the manufacturer, there is a potential bias. Study participants were randomised using permuted block randomisation and assigned to intervention and control group by a doctor who was not involved in the treatment or evaluation. All patients underwent assessment by the lead researcher. The SNRB procedure was performed by skilled doctors who were not involved in this study. All study investigators, hospital staff, and patients were blinded on treatment allocation information. Participants received respective intervention and all assessments were done at similar time for both groups. An intention-to-treat analysis was conducted and there were four participants loss to follow-up (8.3%) among the 48 participants. Outcomes were analysed and selective reporting was considered to have low risk of bias as all pre-specified outcomes were reported and analysed. Funding by the manufacturer could be a source of bias. This could lead to overestimation of benefits or underestimation of harms of HA-CMC therapy.[25]

(b) Shoulder

Rotator cuff tears

Jiang X et al. (2023) received an overall low risk of bias, indicating rigorous methodology. The study conducted electronic searches across PubMed, Embase, and the Cochrane Library database, along with searching grey literature from 2003 to 2022 without language limitations. The review adhered to pre-specified clinical questions and inclusion criteria for study eligibility. Quality assessment of trials was independently conducted by two reviewers, with resolution of disagreements by a third independent author. The Cochrane Collaboration tool was utilised to evaluate bias risk, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method was employed to classify evidence quality. The study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The surface under the cumulative ranking curve (SUCRA) was used to calculate the probabilities of each treatment and publication bias was assessed using funnel plots.[20]

In contrast, Osti L et al. (2015) was rated to have an overall high risk of bias, particularly in selection and attrition bias. Six electronic databases (PubMed, Medline, Ovid, Cochrane Reviews Google Scholar and Embase) were systematically searched and included articles up to August 2014 in English. The review had pre-specified its clinical question and inclusion criteria for study eligibility but lacked detail in quality assessment, statistical heterogeneity evaluation, and sensitivity analyses. Two reviewers independently performed a quality assessment of the trials, and a trained orthopaedic surgeon with special interest in shoulder surgery and sports disorder had final decision in cases of disagreement. Although data extraction was presented in a table and process/results depicted in a flow chart, reporting of outcome data was poor.[21]

Both single arm open-label clinical trial, Tack P et al. (2022) had high risk of bias and Costantino C et al. (2009) was rated with some concerns.

Adhesive capsulitis (Frozen shoulder)

Mao B et al. (2022) were rated to have an overall low risk of bias. They conducted electronic searches across four databases, covering data up to January 15, 2022. Their review had predefined clinical questions and inclusion criteria to determine study eligibility. Two independent reviewers assessed the study quality, with any disagreement resolved by a third senior author. The study adhered to the guidelines outlined in the Cochrane Handbook of Systematic Reviews and followed the reporting standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Evaluation of bias risk was carried out using The Cochrane Collaboration tool, and the analysis utilised Review Manager (RevMan) software, Version 5.3. The study also included reports on statistical heterogeneity and sensitivity analyses.[15]

On the other hand, Papalia R et al. (2017) received a high risk of bias rating. Electronic searched were conducted across four databases up to February 24, 2017. The review established its clinical question and defined inclusion criteria for determining study eligibility. Two reviewers evaluated the full-text articles of eligible trials, and data were extracted and summarised into tables. The studies selection process was presented in a PRISMA flow diagram. The included studies comprised a variety of study designs, including RCTs, prospective and retrospective cohort studies, and cross-sectional studies, with evidence level ranging from I to IV. However, the review did not provide detailed information on the assessment of quality of included studies, statistical heterogeneity and sensitivity analyses.[22]

Lastly, Maund E et al. (2012) also had an overall low risk of bias rating. Nineteen electronic databases and other sources were searched up to March 2012 without language restrictions. Similar to the other studies, Maund et al. predefined its clinical question and inclusion criteria for study eligibility. Two authors independently screened relevant studies, with one author responsible for data extraction and study quality assessment, which was then verified by a second reviewer. Studies were assessed using a checklist. For randomised and non-randomised trials, assessments were based on the Centre for Reviews and Dissemination (CRD) guidance. The quality of economic evaluation was assessed using a modified version of the Drummond checklist. The analysis comprised a narrative synthesis and pair-wise meta-analysis, with a mixed-treatment comparison (MTC) was also conducted. Pair-wise meta-analysis was based on RevMan 5.[23]

Rotator cuff / Supraspinatus tendinopathy

Lin MT et al (2019) were assessed to have an overall low risk of bias in their study. They conducted electronic searches across PubMed, Embase, Scopus, and Cochrane Library

databases, without language restrictions, up to September 31, 2017. Additionally, they searched relevant grey literature using ClinicalTrials.gov, OpenSIGLE, and the New York Academy of Medicine Grey Literature Report. The review established its clinical question and pre-specified inclusion criteria for study eligibility. Two authors independently assessed and reviewed relevant studies, resolved disagreements through consensus-based discussion with the corresponding author. The quality of RCTs was evaluated independently by both authors using the Cochrane Risk of Bias Tool. Analysis was performed using Stata 14.0 and Review Manager 5.3. The study included reports on statistical heterogeneity and sensitivity analyses.[17]

Rezasoltani Z et al. (2021) have an overall high risk of bias in their study. Participants were subjected to block randomisation and assigned to either the intervention or control group. However, neither the investigators, clinicians, nor the patients were blinded to the group assignments. The intervention group received a single injection dose, while the control group underwent 12 weeks of physiotherapy sessions, indicating unequal treatment between the groups. Nonetheless, all assessments were conducted at similar time for both groups, with a small loss to follow-up of five participants (8.9%). The study selective reporting demonstrated a low risk of bias, as all pre-specified outcomes were reported and analysed.[26]

On the other hand, Mohebbi R et al. (2021) achieved an overall low risk of bias. They ensured adequate random sequence generation and allocation concealment, and all involved patients, investigators, and data analyst were blinded. Baseline comparability between the intervention and control groups was maintained. Moreover, outcomes were analysed for all participants, and the study exhibited low risk of bias in selective reporting, as all pre-specified outcomes were reported and analysed.[27]

Merolla G et al. (2013) exhibited an overall high risk of bias. The consecutive assignment method of the first half and second half was utilised for grouping. The blinding process was not possible, for the surgeons performing the treatment procedure or the physiotherapist in the control group. Similar to Rezasoltani et al., participants received different treatments, with the intervention group received two injection doses and the control group underwent standard protocol of physiotherapy for 30 days. However, assessments were conducted concurrently for both groups, with only a minor loss to follow-up of two patients (4%). All pre-specified outcomes were reported and analysed, indicating low risk of bias in selective reporting.[28]

Supraspinatus tendinitis and tendinosis

Finally, Özgen M et al. (2012) and Meloni F et al. (2008) were both rated as having a high risk of bias. While both studies mentioned randomisation, they failed to describe the process adequately. Additionally, all participants were aware of the intervention they received, without blinding. However, the two groups received equal treatment, with assessments conducted at similar time. Despite reporting all pre-specified outcomes, these studies exhibited a high risk of bias overall.[29, 30]

5.1 EFFICACY / EFFECTIVENESS

Most of the included studies assessed the treatment effectiveness by measuring **pain relief and improvements in limb functionality**. Additionally, the studies also evaluated efficacy kinetics, quality of life and adverse events as integral components of the other outcome measures.

5.1.1 Spine

(a) Lumbar spinal stenosis

A double-blinded randomised controlled trial was conducted by Ko S et al. (2021) with the aim to compare the potency of hyaluronic acid-carboxymethylcellulose (HA-CMC) solution versus that of corticosteroids regarding lower leg radiating pain (LLRP) improvement, functional outcome, and quality of life. The study was carried out from August to December 2019. **HA-CMC solution was used because it is the only HA solution that can be used in spine approved by the Korean Food and Drug Administration.** Forty four patients who complain about having LLRP due to lumbar spinal stenosis and do not have neurological symptoms requiring surgery were enrolled. The participants were randomised and assigned into Group A (local anaesthetics and corticosteroid) as the control group (n=22), and Group B (local anaesthetics and HA-CMC) as the intervention group (n=22). The cocktail injection was administered through selective nerve root block (SNRB), conducted on an outpatient bases by **a skilled surgeon.** Follow-up assessment at two, six, and 12 weeks after SNRB were carried out in the clinic by a trained nurse who was unaware of the study. Patients were kept blind to their treatment allocation. The degree of symptomatic improvement was evaluated at baseline, post-SNRB at two weeks for short-term effects, and at six and 12 weeks for long-term effect. The assessed outcomes included pain measured by the Visual Analogue Scale (VAS) score, the Oswestry Disability Index (ODI) for functional outcomes, and the Short-Form-36 (SF-36) for quality of life. The initial VAS scores in the control group (Group A) and the intervention group (Group B) were (mean ± SD) 8.80 ± 1.28 and 8.70 ± 1.38, respectively. The 95% confidence interval of the difference in VAS score improvement between the two groups in all time periods was within VAS 5.0, which representing the minimum clinically relevant difference (Table 1). Across all time intervals, there were no statistical significant differences observed between the two groups concerning VAS scores and their changes over time, ODI scores and improvements over time, as well as SF-36 physical component scores (PCS) and SF-36 mental component scores (MCS) (all with p-values greater than 0.05).[24]

(b) Lumbar radiculopathy

Ko S et al. (2019) had conducted a double-blind randomised controlled trial from January 1st to March 31st, 2016 to determine if **HA-CMC solution injection** could reduce the occurrence of rebound pain at three days to two weeks after SNRB in patients with radiculopathy compared with injection with corticosteroids and local anaesthetics alone. Patients with lumbar foramina stenosis confirmed by magnetic resonance imaging (MRI), with the Leeds assessment of neuropathic symptoms and signs (LANSS) score of seven or more, and radiating pain VAS score of five or above were selected. A total of 48 patients were enrolled and randomised into two groups: Guardix cocktail injection group (n=24) and control group cocktail injection (n=24). The cocktail injection was administered through SNRB procedure performed by **skilled doctors** who were not involved in the study. Patients were blinded to the treatment regime; however, there was no mention of blinding regarding the assessors. Assessments were conducted at baseline, two, six, and 12 weeks after SNRB. Pain was assessed using the VAS score, while functional outcomes were evaluated through ODI, Roland Morris Disability Questionnaire (RMDQ), and Short Form-36. The baseline VAS score of radiculopathy in the control group and the intervention (Guardix) group were (mean ± SD) 7.70 ± 1.26 and 7.24 ± 1.38, respectively. Two weeks post-SNRB, the VAS score was 4.19 ± 1.32 in the control group and 2.43 ± 1.24 in the intervention group, indicating a significantly lower pain score in the Guardix group (MD: -1.75; 95% CI: -2.53 to -0.97, $p<0.05$). However, no significant differences in pain improvement were observed at six and 12 weeks post-SNRB. Functional outcomes also demonstrated no significant differences at six or 12 weeks after the procedure (all, $p>0.05$) (Table 1).[25]

Table 1 presents a summary of the findings from the included studies. Selective nerve root block (SNRB) is acknowledged as an effective short-term pain control treatment. These studies demonstrated that IA HA-CMC solution could be an alternative to corticosteroid in SNRB for spinal stenosis and lumbar radiculopathy. However, interpreting the results should be with caution due to the limited population size and dependent on a single study for both conditions. Further RCTs are necessary to assess the effectiveness of HA and determine optimal dosing.

Table 1: Outcomes of included studies for spinal disorders

Author / Study design	No. of patients	Pain			Functional improvement		Quality of Life
		Short-term (2 weeks)	**Mid-term (6 weeks)**	**Long-term (12 weeks)**	**Mid-term (6 weeks)**	**Long-term (12 weeks)**	**6 weeks and 12 weeks**
Ko S et al. (2021) RCT Group A (Control): LA + CS Group B (Intervention): LA + HA-CMC	44	VAS scores improvement compared to baseline (mean ± SD): Group A: 4.00 ± 2.41 Group B: 3.80 ± 2.12 (95% CI: -1.65 to 1.25, p=0.78)	VAS scores improvement compared to baseline: Group A: 5.10 ± 2.13 Group B: 4.60 ± 3.60 (95% CI: -2.39 to 1.39, p=0.60)	VAS scores improvement compared to baseline: Group A: 4.90 ± 2.40 Group B: 5.45 ± 2.37 (95% CI: -0.98 to 2.08, p=0.41)	ODI improvement compared to baseline: Group A: 0.65 ± 7.05 Group B: 1.20 ± 6.24 (95% CI: -3.71 to 4.81, p=0.80)	ODI improvement compared to baseline Group A: 4.80 ± 9.28 Group B: 5.10 ± 7.41 (95% CI: -5.08 to 5.68, p=0.91)	No significant difference between the two groups in the SF-36 PCS and SF-36 MCS (all, p>0.05)
		No significant differences (all, p > 0.05)			No significant differences (all, p > 0.05)		
Ko S et al. (2019) RCT Control group: LA + CS Intervention group: Guardix cocktail (LA + HA-CMC)	48	Statistically significant VAS score improvement compared to baseline (mean ± SD): Control group: 4.19 ± 1.32 Intervention group: 2.43 ± 1.24 (MD: -1.75; 95% CI: -2.53 to -0.97, p<0.05]	No significant differences in pain improvement at six and 12 weeks post-SNRB		No significant differences of functional outcomes at six or 12 weeks after the procedure (all, p > 0.05)		-

LA: local anaesthesia, CS: corticosteroid, HA-CMC: hyaluronic acid-carboxymethylcellulose, VAS: Visual Analogue Scale, ODI: Oswestry Disability Index, SF-36: Short Form-36 Questionnaires, PCS: Physical Component Score, MCS: Mental Component Score, SD: standard deviation, MD: mean difference, 95% CI: 95% confidence interval, SNRB: selective nerve root block

5.1.2 Shoulder

This report encompasses various shoulder conditions, namely shoulder rotator cuff tears, adhesive capsulitis (frozen shoulder), supraspinatus tendinopathy, tendinitis, and tendonitis.

(a) Rotator cuff tears

Jiang X et al. (2023) conducted a systematic review and network meta-analysis to evaluate the clinical effectiveness of three injection therapies – namely, corticosteroid, sodium hyaluronate (SH), and platelet-rich plasma (PRP) – in managing patients with rotator cuff tears. They performed electronic searches across three databases, complemented by grey literature searches, and evaluated articles published from 2003 to 2022 with no language restrictions. The study included randomised controlled trials and prospective trials involving adults diagnosed with any type of **degenerative, traumatic, partial or full-thickness rotator cuff tears**. The selected trials employed at least two arms of non-operative injection therapies and measured treatment effects in terms of pain reduction and improvement in shoulder function. A total of 16 studies, consisting of 12 RCTs and four prospective studies, involving 1,115 participants were included for analysis. In this study, the short-term effect was determined by assessments conducted at a time point of less than 6 months, whereas long-term effect were characterised at a time period equal to or more than 6 months. Sixteen studies examined the short-term effects, while 11 studies investigated long-term effects. Corticosteroid, PRP and SH showed significant superiority in the short-term and long-term efficacy of pain relief over the control group. Among the three injection therapies, sodium hyaluronate produced a greater reduction in the VAS score (MD: -2.80; 95% CI: -3.91 to -1.68) for short-term effects. For long-term effects, PRP therapies showed better improvement in pain relief compared to SH (MD: -0.79; 95% CI: -1.31 to -0.28). However, the three injection therapies only demonstrated functional improvement superiority over the control group only for the short-term effect. In the short-term, individuals received SH reported greater improvement in the Constant score (MD: 19.17; 95% CI: 12.29 to 26.05). For long-term functional improvement, only PRP therapy demonstrated a statistically significant benefit over the control group (MD: 11.11; 95% CI: 0.53 to 21.68). To rank the probability of the three treatments in pain relief and functional improvement in the short-term or long term, the researchers conducted the surface under the cumulative ranking curve (SUCRA) analysis. **In the short-term**, SH appeared to be the most effective injection treatment for pain relief (SUCRA score: 89.9) and functional improvement (SUCRA score: 86.4). **For the long-term**, PRP injection seemed to be the superior choice for both pain relief (SUCRA score: 100.0) and functional improvement (SUCRA score: 89.2).[20]

In 2015, Osti L et al. conducted a systematic review aimed to assess the feasibility, safety, and efficacy of the injection of hyaluronic acid (HA) for rotator cuff tears. The

authors searched six electronic databases, and only papers published in English up to August 2014 were selected. The inclusion criteria comprised randomised controlled trials, prospective, and retrospective studies that reported on clinical and functional outcomes in **patients who had received sub-acromial or intra-articular HA injections for management of rotator cuff tears**. A total of 11 articles involving 1,102 patients were subjected to analysis. Various types of HA, including low or medium molecular weight, were utilised across the studies. The number of HA injections administered varied, ranging from one or two to three injections, or one injection every five weeks. The duration of follow-up ranged from one week to four years after the injection. In all the studies, there was an observed improvement in the VAS score following HA treatment. Two studies comparing **HA versus methylprednisolone acetate injections** reported HA yielded better clinical results and symptoms improvement, particularly in terms of enhancing range of motion and shoulder function. Additionally, four studies comparing **HA versus phosphate-buffered saline injections** noted substantial improvement in clinical symptoms, recovery, and pain relief. Two studies evaluating the use of **HA compared to physical therapies** concluded that HA injections were safe and effective for patients with rotator cuff pathology.[21]

Tack P et al. (2022) conducted a prospective, single-arm, open-label clinical trial to investigate hyaluronic acid as an alternative treatment for rotator cuff tears. Patients diagnosed with **symptomatic degenerative full-thickness rotator cuff tear**, confirmed through arthro-computed tomography (CT) between September 2014 and June 2016, were included in the study. Three doses of HA injections were administered at a 2-week interval by a **skilled physician** using an anterior approach. Prior to the HA injection, 5-10 cc of 2% lidocaine was injected into the joint as an analgesic. The study initially enrolled 72 patients. However, eight patients (11%) were lost to follow-up and 10 patients were excluded due to engagement in other treatments for their shoulder pathology during the study period. The study reported that 84% (54 patients) of the study participants did not require additional treatment for their shoulder pathology. Hence, a total of 54 patients were evaluated at the final 60-month (five years) follow-up. Shoulder function and quality of life outcomes were assessed at baseline (before the first HA injection), 3, 6, 12, and 60 months. Three validated Dutch questionnaires were utilised for shoulder function assessment: the Oxford Shoulder Score (OSS), Disabilities of the Arm, Shoulder and Hand (DASH), and Constant-Murley Score (CMS). The OSS showed a significant increase in shoulder function after treatment at all-time points (3, 6, 12, 60 months) compared to baseline ($p=0.001$). The DASH score exhibited a significant difference between baseline and 6, 12, and 60 months ($p<0.05$), with no significant difference found between baseline and 3 months evaluation. ($p=0.211$). The involvement of the subscapularis tear significantly influenced the outcomes, resulting in inferior results ($p=0.015$). The CMS showed no significant difference after treatment at each evaluation (3, 6, 12, 60 months), with the involvement of a subscapularis tear lead to a significantly lower CMS ($p=0.047$). Quality of life was assessed using the Short Form-36, and the SF-36 Physical Component Score (PCS) demonstrated a significant

increase after treatment at each evaluation (3, 6, 12, 60 months) compared to baseline (p=0.001). While the SF-36 Mental Component Score (MCS) showed a significant increase in results only for the long term at the 60-month evaluation (p=0.001).[31]

In 2009, Costantino C et al. conducted a prospective, single-arm, open-label clinical trial aimed at assessing the effectiveness of the infiltrative treatment with hyaluronic acid, followed by a targeted rehabilitative programme in elderly patients ineligible for surgical intervention. The study enrolled elderly patients experiencing sharp pain, significant shoulder range of motion limitations, and loss of autonomy in daily life activities. Twenty-two **elderly patients with a non-traumatic tendon rupture**, confirmed through echography or MRI imaging, coexisting debilitating conditions, and refusal of surgical options were included. The treatment protocol involved administering three doses of intra-articular hyaluronic acid infiltration weekly through anterior access. Subsequently, participants underwent 20 sessions of targeted rehabilitative intervention including passive and active assisted kinesiotherapy, following HA infiltration. Pain assessments using the VAS and evaluations of shoulder function through Constant-Murley and the Shoulder Rating Questionnaire scores were conducted at 1, 3, and 6 months. Results revealed statistically significant improvement in pain reduction, range of motion in both shoulder flexion and abduction, and autonomy in daily life activities at the third month of treatment ($p<0.0005$). The significant pain reduction, enhanced shoulder range of motion, and improved daily life activities observed at the first month persisted to improve or maintain until the sixth month follow-up. The sustained reduction of pain positively influenced the improvement in range of motion and daily life activities in the long-term. Patients reported able to resume their daily life activities.[32]

The results of the studies included are outlined in Table 2. These studies indicated that IA HA injections effectively reduced pain, enhanced shoulder function, and improved the quality of life in patients with rotator cuff tears. However, HA injections demonstrated a short-term benefit lasting less than 6 months, whereas platelet-rich plasma injections may provide favourable outcomes in long-term follow-up of over 6 months. Combining IA HA infiltration with rehabilitative treatment resulted in superior effective results.

Table 2: Outcomes of included studies for rotator cuff tears

Author / Study design	No. of studies (no. of patients)	Pain		Functional improvement		Quality of Life
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)	
Jiang X et al. (2023) SR & network MA	16 studies (1,115)	11 studies with 775 patients CS, PRP, SH showed significant superiority over the control group. **SH showed a greater reduction in the VAS score** (MD: -2.80; 95% CI: -3.91 to -1.68)	5 studies with 395 patients CS, PRP, SH showed long-term efficacy over the control group. PRP injection had the greatest reduction in VAS score (MD: -4.50; 95% CI: -4.97 to -4.03) while SH VAS score was (MD:-3.71; 95% CI: -4.18 to -3.24) **PRP have better improvement in pain relief than SH** (MD: -0.79; 95% CI: -1.31 to -0.28)	10 studies with 648 patients CS, PRP, SH showed superiority over the control group. **SH showed greater improvement in the Constant score** (MD: 19.17; 95% CI: 12.29 to 26.05)	8 studies with 589 patients Only **PRP therapy** had a statistically significant benefit over the control group (MD: 11.11; 95% **CI: 0.53 to 21.68**)	-
Osti L et al. (2015) SR	11 studies (1,102)	Showed HA injection reduced pain	-	Showed HA injection improved shoulder function	-	-
Tack P et al. (2022) Prospective study **[Intra-articular HA injection]**	(72)	-	-	Significant increase in shoulder function after **HA injection** at 3 months only in the OSS score (p=0.001), not in the DASH and CMS.	Significant increase in shoulder function after **HA injection** at 6, 12, 60 months in the OSS (p=0.001) and DASH score (p<0.05), not in CMS	SF-36 PCS showed significant increase at 3, 6, 12, 60 months after **HA injection** (p=0.001). SF-36 MCS only showed significant increase at 60 months (p=0.001).
Costantino C et al. (2009) Prospective study **[Intra-articular HA infiltration + rehabilitation]**	(22)	At 1, and 3 month : Significant improvement in pain reduction (p<0.0005)	At 6 month: Significant improvement in pain reduction.	At 1, and 3 month : Significant improvement in shoulder flexion & abduction range of motion (p<0.0005)	At 6 month: Significant improvement in shoulder flexion & abduction range of motion.	At 1, 3 and 6 month: Significant improvement in daily life activities.

CS: corticosteroid, PRP: platelet-rich plasma, SH: sodium hyaluronate, HA: hyaluronic acid, VAS: Visual Analogue Scale, OSS: Oxford Shoulder Score, DASH: Disabilities of the Arm, Shoulder and Hand, CMS: Constant-Murley Score, SF-36: Short Form-36, PCS: Physical Component Score, MCS: Mental Component Score,

(b) Adhesive shoulder capsulitis (Frozen shoulder)

Mao B et al. (2022) conducted a systematic review and meta-analysis of randomised controlled trials to investigate whether intra-articular administration of hyaluronic acid facilitates symptomatic pain relief and functional recovery in **patients diagnosed with frozen shoulder**. Electronic searches were performed across four databases, encompassing data up to January 15, 2022. The study included RCTs comparing intra-articular HA injection with other non-surgical treatments (such as corticosteroid injection and physical therapy) in patients diagnosed with frozen shoulder or stiff shoulder. The investigation focused on outcome measures related to pain relief, improvement of range of motion (ROM), and functional recovery. A total of seven studies involving 504 patients were included in the analysis. The follow-up periods of the studies ranged from 3 to 6 months, except for one study with a duration of four weeks. Four studies underwent meta-analysis to assess the effect of pain relief. The results indicated that hyaluronic acid injection did not demonstrate superior efficacy in pain relief compared to other therapies (p=0.75). Regarding the improvement of range of motion, the HA injection group showed better improvements in external rotation (p=0.003), but no significant differences were observed in shoulder abduction (p=0.69) and flexion (p=0.33), compared with the control group. Functional scales were evaluated using Shoulder Pain and Disability Index (SPADI), Constant score, and American Shoulder and Elbow Surgeons (ASES). For SPADI, three studies demonstrated that the control group had a better improvement than the HA group (p=0.01), with low heterogeneity (I^2=10%). Three studies measuring the Constant score showed no significant difference between the HA and control groups (p=0.36), and in ASES assessment, two studies indicated no difference between the HA and control groups (p=0.76).[15]

Papalia R et al. (2017) conducted a systematic review to evaluate the best evidence regarding the effectiveness of intra-articular HA injections in the treatment of **primary adhesive capsulitis** (AC). Four electronic databases were searched and evaluated articles published up to February 24, 2017. Unpublished trials were identified through the ClinicalTrials.gov registry. Articles in English, Spanish, French and German involving human subjects were included. The selected studies were of various designs, including RCTs, prospective and retrospective cohort studies, and cross-sectional studies, with evidence level ranging from 1 to IV. The studies included patients who underwent treatment for primary AC or had diabetes mellitus, received intra-articular glenohumeral or joint HA injection, and reported clinical outcomes post-HA injection, comparing intra-articular HA injection with a control group. The control group consisted of physical therapy, corticosteroid injection, or home stretching and Codman's exercise. A total of seven studies involving 429 shoulders were analysed. The majority of studies used high molecular weight HA. Two intra-articular modes of administration were observed: five studies used blind technique, and two studies utilised ultrasonography guidance. Overall, the results indicated that intra-articular HA injections led to improvements in

range of motion, Constant scores, and pain in patients with adhesive capsulitis. The outcomes of HA injections were found to be comparable to corticosteroid injections in terms of clinical outcomes and range of motion. Hyaluronic acid injections may have a role in early mobilisation and preventing shoulder immobilisation. However, the heterogeneity of treatments used in the studies makes it challenging to draw a definite conclusion.[22]

Maund E et al. (2012) conducted a health technology assessment (HTA) to evaluate the clinical effectiveness and cost-effectiveness of treatment for **primary frozen shoulder**. Their objectives were to determine the most appropriate intervention on the stage of the condition and to identify any existing gaps in the evidence. The study included randomised controlled trials that investigated the use of sodium hyaluronate injection in patients with primary frozen shoulder (with or without diabetes). The evaluated clinical effectiveness studies covered a range of interventions, including steroid injection, sodium hyaluronate (SH), supervised neglect, physical therapy, acupuncture, manipulation under anaesthesia (MUA), distension and capsular release. In total, 31 clinical effectiveness studies and one economic evaluation study were included in the analysis. Focusing specifically on the review of sodium hyaluronate, three RCTs were reviewed, comprising two two-armed trials and one four-armed trial. All three trials were assessed as having a high risk of bias. At the time of the HTA review, sodium hyaluronate was not licensed for use in frozen shoulder. Among the findings, only one study reported a significant reduction in pain at 6 months when using SH in combination with steroid and physiotherapy compared to the combination of steroid and physiotherapy (SMD -0.78; 95% CI: -1.50 to -0.06). The same study also reported a significant improvement in internal rotation with the SH combination (MD 23.70°; 95% CI: 13.44° to 33.96°). Another study indicated a benefit in function and disability at 3 months with SH compared to home exercise (MD 8.90; 95% CI: 2.62 to 15.18), although no such benefit was observed with physiotherapy or steroid. The study also reported significant short-term improvement in passive external rotation and abduction with SH compared to home exercise and physiotherapy, but not steroid injection. The final study reported no evidence of a benefit for external rotation with SH compared to steroid injection. Consequently, the available evidence was insufficient to draw a conclusion regarding the effectiveness of sodium hyaluronate for treating primary frozen shoulder.[23]

The findings of the studies included can be found in Table 3. In summary, the studies suggest potential short-term benefits of IA HA injections for patients with frozen shoulder lasting less than 6 months. These injections showed comparable effectiveness to intra-articular corticosteroid injections and other non-surgical treatments in terms of relieving pain and improving range of motion. Hyaluronic acid injections may play a role in early mobilisation and preventing shoulder immobilisation in frozen shoulder cases. Additionally, combining physiotherapy with these injections could offer better short-term advantages for patients.

Table 3: Outcomes of included studies for adhesive shoulder capsulitis

Author / Study design	No. of studies (no. of patients)	Pain		Range of motion		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
Mao B et al. (2022) SR & MA of RCTs **[HA injection vs other non-surgical therapy]**	7 studies (504)	HA did not yield better pain relief compared with other therapies (p=0.75)	-	HA showed better improvement in external rotation (p=0.003). Not in shoulder abduction (p=0.69) and flexion (p=0.33)	-	SPADI: Control group had better improvement than HA (p=0.01, I^2=10%) Constant score and ASES: no significant difference between HA and control group.	-
Papalia R et al. (2017) SR **[HA injection vs Control]**	7 studies (429 shoulders)	Pain improved post-HA injection compared to control.	-	ROM improved in HA injection compared to control. HA had equivalent ROM outcome with corticosteroid injection.	-	Constant score improved in HA injection compared to control. HA had equivalent clinical outcomes with corticosteroid injection.	-
Maund E et al. (2012) HTA	3 studies (140 patients with 145 shoulders)	***Calis 2006:*** significant improvement in pain severity at 3 months in all groups (p<0.001). ***Takagishi 1996:*** No significant difference with SH compared to steroid.	***Rovetta 1998:*** A significant decrease in pain at 6 months with SH + steroid + physiotherapy compared with steroid + physiotherapy (SMD -0.78; 95% CI: -1.50 to -0.06)	***Calis 2006:*** At 3 month • Significant improvement in SH group vs no treatment (home exercise only) group in both **passive external rotation and passive abduction** • Significant improvement in physiotherapy group vs SH group in both **passive external rotation and passive abduction** • No significant difference in passive external rotation or	***Rovetta 1998:*** At 6 months • Significant improvement in **internal rotation** with SH + Steroid + physiotherapy vs steroid + physiotherapy • No significant difference in external rotation or abduction between the two groups.	***Calis 2006:*** At 3 month, in Constant score: • Significant improvement with SH vs no treatment (home exercise only) • No significant difference between SH and physiotherapy • No significant difference between SH and steroid injection	-

Author / Study design	No. of studies (no. of patients)	Pain		Range of motion		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
				passive abduction between SH group and steroid injection group. ***Takagishi 1996:*** At 5 weeks: No significant difference for external rotation in both SH group and steroid group			

HA: hyaluronic acid, SH: sodium hyaluronate, CS: corticosteroid, ROM: Range of motion, SPADI: Shoulder Pain and Disability Index, ASES: American Shoulder and Elbow Surgeons, ROM: Range of movement, MD: Mean Difference, 95% CI: 95% Confidence Interval

(c) Rotator cuff / Supraspinatus tendinopathy

Lin MT et al. (2019) conducted a comprehensive systematic review, including pairwise and network meta-analysis of RCTs to compare the effectiveness of various injection therapies for **rotator cuff tendinopathy**. They performed electronic searches across four databases and evaluated published and unpublished RCTs up to September 31, 2017. Inclusion criteria involved adult patients diagnosed with rotator cuff tendinopathy, confirmed clinically or through imaging, and allocated into groups receiving at least two different injection therapies (including corticosteroid, non-steroidal anti-inflammatory drugs (NSAIDs), HA, botulinum, PRP, prolotherapy, and placebo). Of the 23 RCTs included in the qualitative synthesis, 18 were incorporated into the meta-analysis. For hyaluronic acid specifically, were analysed using four RCTs in the qualitative synthesis and three RCTs in the meta-analysis (comparing HA vs placebo or steroid). Follow-up outcomes were categorised into short term (3-6 weeks), medium term (12 weeks), and long term (over 24 weeks). In a pairwise meta-analysis, corticosteroid injections were found to be more effective in the short term for both pain reduction and functional improvement. The network meta-analysis revealed that in the long term, prolotherapy significantly reduced pain compared to placebo (SMD: 2.63, 95% CI: 1.88 to 3.38), while PRP significantly improved shoulder function compared to placebo (SMD: 0.44, 95% CI: 0.05 to 0.84). When comparing HA to placebo, no significant difference were observed in pain reduction or functional improvement. The meta-analysis concluded that injections of botulinum, HA, and NSAIDs were all ineffective for the treatment of rotator cuff tendinopathy. For patients with rotator cuff tendinopathy, corticosteroid plays a role in the short term but not in long term pain reduction and functional improvement. By contrast, PRP and prolotherapy may yield better outcomes in the long term. In this meta-

analysis, injections of botulinum, HA, and NSAID were all ineffective for treatment of rotator cuff tendinopathy.[17]

Rezasoltani Z et al. (2021) conducted a randomised controlled trial to assess the effectiveness of low molecular-weight hyaluronic acid compared to physiotherapy in patients with **supraspinatus tendinopathy**. Fifty-six participants underwent block randomisation into the HA group and physiotherapy (PT) group. The HA group received a single subacromial HA injection performed by an experienced clinician using an anterolateral approach under ultrasound guidance. The PT group underwent three sessions per week for 12 weeks, totalling 36 sessions. The initial 12 sessions consisted superficial heat, transcutaneous electrical nerve stimulation (TENS), and pulsed ultrasonography, followed by 24 sessions of shoulder muscle stretching exercises. Assessments of shoulder pain, function, range of movement, and quality of life (QOL) were conducted at baseline, 1, 4, and 12 weeks. The baseline VAS mean (standard deviation) pain scores were comparable between the groups: 7.11 (1.64) in HA group and 7.57 (2.29) in the PT group, p=0.424. Both groups showed a consistent decrease in pain scores throughout the study, with the HA group experienced a steeper decline. The within-group differences in HA group were observed, with large effect sizes. In the between-group analyses at baseline to 12 weeks: HA was more effective in reducing shoulder pain at rest and during activities (both p<0.01, effect size=0.52 and 0.68, respectively). At 12 weeks, both interventions demonstrated similar decreases in the total DASH scores indicating comparable improvements in patients' disability (p=0.196). The HA group showed superior improvement in shoulder motion, particularly in flexion, abduction, adduction, and internal rotation (all, p<0.05), while both groups were comparable in extension and external rotation. Both interventions showed benefits in improving QOL, but HA was more effective in enhancing the physical, psychological, and environmental domains of World Health Organization Quality of Life-Bref (WHOQOL-Bref) questionnaire.[26]

In a triple-blind randomised controlled trial by Mohebbi R et al. (2021), the clinical effectiveness of low-molecular weight (LMW)-HA and high-molecular weight (HMW)-HA was assessed in patients with **rotator cuff tendinopathy**. A total of 56 patients were randomly assigned to the HMW-HA group (n=28) or the LMW-HA group (n=28). Participants in both groups received a single periarticular injection of either 20 mg (2 ml) HMW-HA 1% (>2,000 kDa) or 20 mg (2 ml) LMW-HA 1% (500-700 kDa), respectively, administered by an experienced clinician using an anterolateral approach under ultrasound guidance. Primary outcome of pain and secondary outcomes including shoulder disabilities, range of movement, and quality of life were assessed at baseline, 1, 4, and 12 weeks post- interventions, with additional pain assessments at 6 months for long-term effects. Both groups were comparable at baseline. Within-group comparisons from baseline to 3 months showed a statistically significant reduction in shoulder pain intensity for both interventions (all, p<0.05), with large effect sizes. HMW-HA and LMW-HA similarly improved shoulder pain at night, during activity, and at rest.

Long-term assessment at 6 months revealed no statistically significant difference in mean pain intensity at night, during activity, and at rest between the two groups. Shoulder disability significantly improved within both groups after the intervention (all, $p<0.01$), but between-group analyses did not revealed any clinically significant differences. In terms of range of movement, both groups showed improvement in shoulder flexion, extension, abduction, adduction, internal rotation, and external rotation (all, $p<0.05$) within-group at 3 months. However, between-group analyses demonstrated comparable results for shoulder adduction, internal rotation, and external rotation. Both groups experienced improvement in QOL, with no significant difference between the groups.[27]

In 2013, Merolla G et al. conducted a non-randomised controlled trial to assess the effectiveness and safety of **subacromial sodium hyaluronate injections** compared to rehabilitation therapy in patients with **chronic rotator cuff tendinopathy**. Fifty adult patients with persistent shoulder pain for at least four months were enrolled, with the first half assigned to the HA group (n=25) and the second half to the physiotherapy group (n=25). The HA group received ultrasound-guided HA injections at baseline and 14 days through the anterolateral, while the physiotherapy group underwent standard physiotherapy three sessions a week for 30 days. Two patients were excluded from the physiotherapy group due to consent refusal at enrolment and lost to follow-up. Pain and shoulder function were assessed at 2, 4, 12, and 24 weeks. At the baseline, the VAS (mean ± standard deviation) pain scores were comparable between the two groups, with values of 7.48 ± 1.61 in HA group and 7.17 ± 1.23 in the physiotherapy group ($p=0.967$). Within the HA group, there was a significant decreased in VAS pain scores at week 2, 4 and 12 (all, $p<0.05$), but not at week 24. A significant reduction in pain was observed when comparing the HA group and the physiotherapy group at weeks 4 (4.12 ± 1.12 versus 6.34 ± 1.18, $p=0.0149$) and week 12 (4.01 ± 1.04 versus 6.17 ± 1.16, $p=0.0168$). Pain sub-scores (night and with activity) decreased significantly at weeks 2, 4, and 12 (all, $p<0.05$), with no significant change at week 24. The physiotherapy group showed significant pain reduction only at week 2 with mean VAS score 4.43 ± 1.26 ($p=0.0103$). Constant-Murley Scores (CMS) and Oxford Shoulder Scores (OSS) significantly improved in the HA group at weeks 2, 4, and 12 (all, $p<0.05$), but not at week 24. In the physiotherapy group, CMS and OSS had significant improvement only at week 2. When comparing HA group to physiotherapy group, no significant differences were observed in CMS scores, but OSS showed significant improvement in the HA group at week 4 and week 12 ($p<0.05$). Patient global assessment indicated good compliance with no serious adverse events during the study. The anterolateral approach injections with ultrasound guidance were safe and well-tolerated by all patients.[28]

(d) Supraspinatus tendinitis

Özgen M et al. (2012) conducted a randomised controlled trial to evaluate the short- and long term effects of **intra-articular sodium hyaluronate** (SH) application compared to conventional physiotherapy in patients diagnosed with **supraspinatus tendinitis and shoulder pain**. Twenty-four patients were randomised into either SH group (receiving IA sodium hyaluronate) or the physical therapy group (receiving TENS, ultrasound and hot pack application) and were informed regarding the intervention received. Intra-articular SH injection was administered to the shoulder joint by posterior approach three times with weekly intervals. Home exercise programmes were recommended to all of the patients in both groups. The patients were evaluated using the Visual Analogue Scale for pain severity, range of motion and functional evaluation parameters at pre-treatment, 3rd week, 3rd month, and 4th year post-treatment. Patient's global effectiveness (PGE) evaluation was performed in the 3rd month and 4th year post-treatment. In the SH group, significant improvement in VAS values were observed at 3 weeks and 3 months post-treatment for pain at night ($p<0.05$) and pain on movement ($p<0.01$). Pain at rest showed significant improvement only at the 4th year ($p<0.05$). Statistically significant recovery in ROM and functional parameters were observed within the SH group ($p<0.05$). When comparing between groups, the SH group demonstrated a significant difference in active abduction at the 3rd month ($p<0.05$). Individuals in the physical therapy group showed no statistically significant differences in passive flexion at the 4th year and in passive external rotation at 3 weeks. However, significant recovery in other evaluation parameters (VAS, ROM, functional evaluation) was observed ($p<0.05$). There was no significant differences between groups in patient's global evaluation at the 3rd month and 4th year ($p>0.05$).[29]

(e) Supraspinatus tendinosis

Meloni F et al. (2008) conducted an open-label prospective study aimed at assessing the effect of **periarticular sodium hyaluronate injections,** guided by echography, in patients with **supraspinatus tendinosis**. Fifty-six patients unresponsive to conventional therapies were randomly assigned to sodium hyaluronate (SH) group and sodium chloride (SC) group. Injections were administered weekly for four weeks, totalling five injections, with the needle reaching the superior limitation surface. Pain assessment using VAS score was conducted at pre-treatment, 4, 12, 24 weeks, and 1 year post-treatment. Symptomatic improvement and patient's satisfaction were assessed through questionnaires. The assessment of range of motion was conducted, however, the specific tool utilised for the evaluation was not specified. In the SH group, the mean VAS score decreased from 8.7 at pre-treatment to 2.8, 3.1, 3.8 and 5.1 at 1, 3, 6, and 12 months, respectively. While the SC group showed no significant pain reduction. Patients in the SC group reported a slight symptom improvement for 24 to 36 hours after each periarticular injection. At 12 weeks, 89% of the SH group reported satisfaction with the treatment, decreasing to 68% at 24 weeks and 1 year. Shoulder

disability improved, and range of motion increased in 89.3% of SH patients after completing five SH injections. There was no significant difference in range of motion among the SC group. Tendon structure showed no substantial differences between the two groups 3, 6, and 12 months post-treatment.[30]

Table 4 provides an overview of the results obtained from the included studies. In summary, corticosteroids show short-term effectiveness but not long-term benefits of pain relief and functional improvement for rotator cuff tendinopathy. Platelet-rich plasma and prolotherapy may offer better long-term outcomes. Botulinum, HA, and NSAID injections were found to be ineffective. However, two studies showed low molecular-weight HA was more effective than physiotherapy, particularly in the first three months, providing successful pain relief. Both high and low molecular-weight HA are effective for tendinopathy, with LMW-HA being more tolerable and recommended as the first choice. Subacromial HA injections provide short-term pain relief and functional improvement up to 3 months, but the effects are not sustained in the long term, and no significant differences are observed compared to physiotherapy.

Both SH injection and physical therapy modalities, along with home exercise programmes, demonstrated similar effects in the short- and long term management of shoulder tendinitis. Sodium hyaluronate injection has a potential management option due to its effectiveness and lower side effects. While in the supraspinatus tendinosis, sodium hyaluronate showed superior effectiveness in alleviating clinical symptoms and restoring functional status compared to the control group. However, it is essential to approach these findings with caution as both supraspinatus tendinitis and tendinosis were each based on a single study with a small study population.

Table 4: Outcomes of included studies for rotator cuff tendinopathy, supraspinatus tendinitis and tendinosis

Author / Study design	No. of studies (no. of patients)	Pain		Range of motion		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
ROTATOR CUFF TENDINOPATHY							
Lin MT et al. (2019) SR & Pairwise and Network MA of RCTs **[HA injection vs CS, NSAIDs, HA, botulinum, PRP, prolotherapy, and placebo]**	23 studies (1,252)	CS injections more effective in short-term (3-6 weeks) pain relief HA injection revealed no significant different compared to placebo.	Prolotherapy more effective in long-term pain reduction (SMD: 2.63, 95% CI: 1.88 to 3.38) HA injection revealed no significant different compared to placebo.	-	-	CS injections more effective in short-term (3-6 weeks) functional improvement. HA injection revealed no significant different compared to placebo.	PRP more effective (SMD: 0.44, 95% CI: 0.05 to 0.84). HA injection revealed no significant different compared to placebo.

Author / Study design	No. of studies (no. of patients)	Pain		Range of motion		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
Rezasoltani Z et al. (2021) RCT **[HA injection vs rehabilitation]**	(51)	Comparison at baseline to 3 months: HA more effective in reducing shoulder pain at rest and during activities (both p<0.01, effect size=0.52 and 0.68, respectively).	-	HA group showed superior improvement in shoulder motion, particularly in flexion, abduction, adduction, and internal rotation (all, p<0.05), while both groups were comparable in extension and external rotation.	-	At 3 months: Both interventions demonstrated similar decreases in the total DASH scores (p=0.196).	-
Mohebbi R et al. (2021) RCT [**HMW-HA vs LMW-HA]**	(56)	At 3 months: HMW-HA reduced shoulder pain at night, during activity and rest (all, p<0.01, Effect size = 0.792, 0.895, and 0.774). LMW-HA reduced shoulder pain at night, during activity and rest (all, p<0.01, Effect size = 0.822, 0.897 and 0.771)**.**	No statistical significant difference in pain intensity at night, during activity, and at rest.	At 3 months: Both groups showed improvement in shoulder flexion, extension, abduction, adduction, internal rotation, and external rotation (all, p<0.05)	-	Shoulder disability significantly improved within both groups (all, p<0.01), but between-group analyses did not revealed any clinically significant differences	-
Merolla G et al. (2013) Non-randomised Controlled Trial **[HA injection vs rehabilitation]**	(50)	HA group: Significant pain decreased at week 2, 4 and 12 (all, p<0.05) Physio group: Significant pain reduction only at week 2 (p<0.05). Compared between groups: significant pain reduction	Both HA and physio groups: No significant pain reduction at week 24.	-	-	HA group: Significant CMS and OSS mean values at week 2, 4 and 12 (all, p<0.05). Physio group: CSS and OSS showed significant functional improvement only at week 2 (p<0.05). Compared between	Both HA and physio groups: No significant functional improvement at week 24.

Author / Study design	No. of studies (no. of patients)	Pain		Range of motion		Functional improvement	
		Short-term (< 6 months)	**Long-term (≥ 6 months)**	**Short-term (< 6 months)**	**Long-term (≥ 6 months)**	**Short-term (< 6 months)**	**Long-term (≥ 6 months)**
		at week 4 and 12 ($p<0.05$).				groups: No significant difference in CMS at all follow-up. OSS showed improvement at week 4 and 12 ($p<0.05$).	
SUPRASPINATUS TENDINITIS							
Özgen M et al. (2012) RCT **[SH injection vs physical therapy]**	(24)	At 3 weeks & 3 months: SH injection group showed significant reduction of pain at night ($p<0.05$) and pain on movement ($p<0.01$)	At 4 years: SH group showed significant improvement of pain at rest ($p<0.05$)	Statistically significant ROM recovery within the SH group ($p<0.05$). SH group at 3 month showed significant difference in active abduction ($p<0.05$).	At 4 years, statistically significant ROM recovery in SH and physical therapy groups.	Statistically significant functional improvement within the SH group ($p<0.05$).	At 4 years, statistically significant ROM recovery in SH and physical therapy groups.
SUPRASPINATUS TENDINOSIS							
Meloni F et al. (2008) Prospective study **[SH injection vs Sodium chloride injection]**	(56)	SH group showed pain reduction: • 8.7 at pre-treatment • 2.8 at 4 weeks (1 month) • 3.1 at 12 weeks (3 months) No significant difference in the SC group	SH group showed pain reduction: • 8.7 at pre-treatment • 3.8 at 24 week (6 months) • 5.1 at 1 year (12 months)	In the SH group, shoulder disability resolved in: • 6 (21.4%) patients after three SH injections • 13 (46.5%) patients after four SH injections • 6 (21.4%) patients after five SH injections. • 3 (10.7%) showed an insufficient improvement of symptoms after SH injections. No significant difference in ROM among the SC group.	-	-	-

HA: hyaluronic acid, SH: sodium hyaluronate, CS: corticosteroid, NSAIDs: non-steroidal anti-inflammatory drugs, PRP: platelet-rich plasma, ROM: Range of motion, MD: Mean Difference, SMD: Standardised Mean Difference, 95% CI: 95% Confidence Interval, HMW-HA: High Molecular-Weight Hyaluronic Acid, LMW-HA: Low Molecular-Weight Hyaluronic Acid,

Tendinitis is an acute inflammation of tendons, commonly following degeneration (tendinopathy).
Tendinosis is the degeneration of tendon's collagen due to prolonged overuse without adequate time for healing and rest, takes a longer time to resolve when compared to tendinitis.

PART II : JOINT DISORDERS AFFECTING THE HIP, KNEE AND ANKLE

6.0 RESULTS

The initial search across the Ovid interface and PubMed yielded a combined total of **7,627** records pertaining to the hip, knee, and ankle joints. However, after the initial screening process, **7,443** records were excluded due to discrepancies in Boolean search terms. Subsequently, **148 records related to the hip, 28 to the knee, and 8 to the ankle** underwent further evaluation. Among these, 170 records were excluded based on screening criteria. Following this, 14 records were identified for retrieval and subsequent assessment of eligibility. Of these, 12 records were excluded for various reasons. Additionally, 11 records were obtained from alternative sources through footnote tracing. Ultimately, after careful evaluation, **11** records were deemed suitable for inclusion in the review. An overview of the search is illustrated in **Figure 4**.

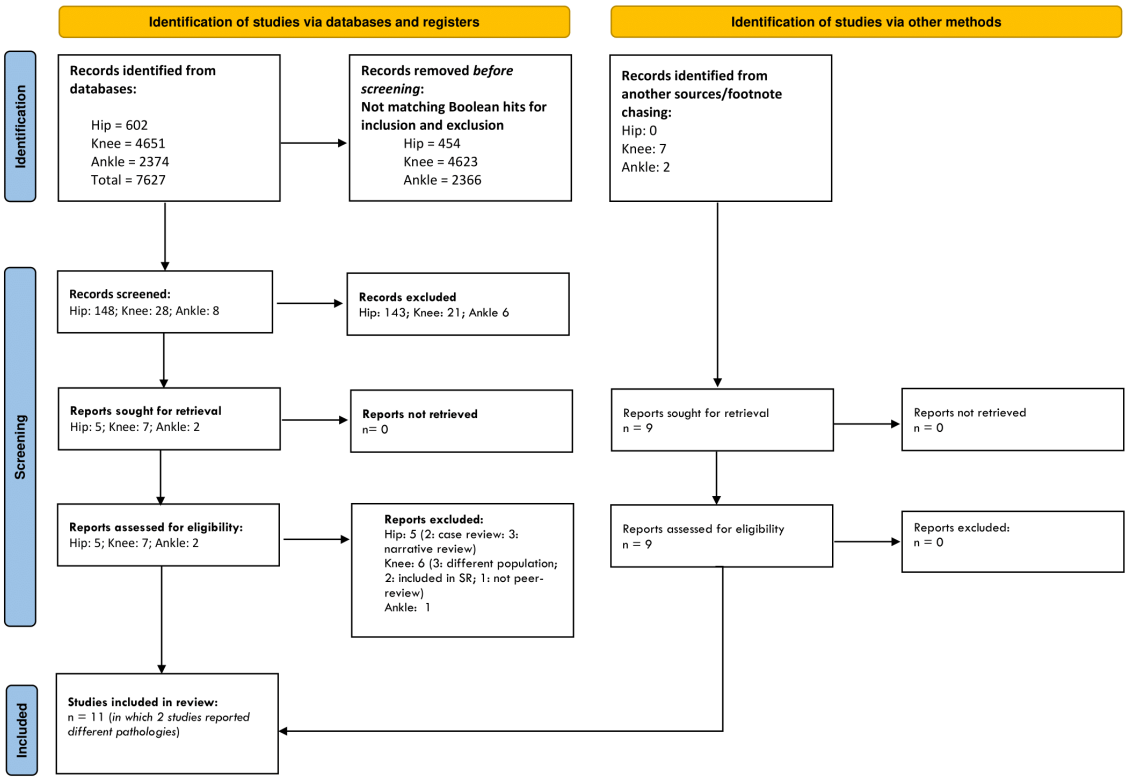

Figure 4: PRISMA 2020 flow diagram of retrieval of articles used in the results for joint disorders affecting the hip, knee and ankle

A systematic search strategy was conducted to evaluate hyaluronic acid effectiveness for various **hip-related conditions** including hip tendonitis, hip ligament or tendon injury, avascular necrosis, or joint contractures. There was, however, no evidence of these conditions that could be retrieved.

Quality assessment of the studies

The risk of bias or quality assessment (methodology quality) of all retrieved literatures was assessed depending on the type of the study design. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias: using the ROBIS tool, the Cochrane Risk of Bias (RoB 2.0), and the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group (non-RCT). All full text articles were graded based on guidelines from the *U.S./Canadian Preventive Services Task Force* ***(Appendix 1)***.

These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

x	High
-	Unclear
+	Low
?	No information

The results of risk of bias for the included studies are summarised in Figure 4.1 to 4.3.

Risk of bias assessment for included systematic review

			Risk of bias				
			D1	D2	D3	D4	Conclusion
Study	Knee	Mao B et al.[39]	+	+	+	+	+
		Tripathy SK et al.[40]	+	+	+	+	+
		D1: Concerns regarding specification of study eligibility criteria. D2: Concerns regarding methods used to identify and/or select studies. D3: Concerns regarding methods used to collect data and appraise studies. D4: Concerns regarding the synthesis and findings. CONCLUSION: Risk of bias in the review.				Judgement x High - Unclear + Low ? No information	

Figure 4.1: Risk of bias assessment for systematic review using ROBIS

Risk of bias assessment for included RCT

			Risk of bias					
			D1	D2	D3	D4	D5	Overall
Study	Knee	Kaux JF et al.[33]	?	+	+	+	+	+
		Astur DC et al.[37]	+	+	+	-	+	-
		Hamawandi SA et al.[38]	+	+	+	+	+	+
	Ankle	Kumai T et al.[41-2017]	+	+	+	+	+	+
		Lynen N et al.[42]	+	+	+	+	+	+

D1: Bias arising from the randomisation process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement

x	High
-	Some concerns
+	Low
?	No information

Figure 4.2: Risk of bias assessment for RCT using RoB 2.0

Risk of bias assessment for included pre-post studies with no control

			Risk of bias												
			D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**Overall**
Study	Knee	Fogli M et al.[34]	+	+	-	-	-	+	+	x	+	+	x	x	x
		Frizziero A et al.[35]	+	+	-	-	-	+	+	x	+	+	-	+	x
		Kumai T et al.[36-2014]	+	+	-	-	x	+	+	x	+	+	x	x	x
	Ankle	Gorelick L et al.[43]	+	+	+	-	x	+	+	x	+	+	+	x	x
		Fogli M et al.[34]	+	+	-	-	-	+	+	x	+	+	x	x	x
		Frizziero A et al.[35]	+	+	-	-	-	+	+	x	+	+	-	+	x

D1: Objective clearly stated
D2: Eligibility criteria clearly described
D3: Participants representative
D4: All eligible participants were enrolled
D5: Sample size sufficiently large to provide confidence in findings
D6: Intervention described clearly
D7: Pre-specified, valid and reliable outcome measures
D8: Blinded assessors
D9: Loss to follow-up after baseline 20% or less? Accounted for loss of follow up
D10: Statistical method for pre/post changes
D11: Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?
D12: If intervention conducted at group level, did statistical analysis take into account of individual level data to determine effects at group level?

Judgement

x	High
-	Unclear
+	Low

Figure 4.3: Risk of bias assessment for Pre-Post studies using the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group

(a) Knee

Knee/patellar tendinopathy

The randomised trial by Kaux et al. (2019) examining platelet-rich plasma (PRP) versus hyaluronic acid (HA) injections for patellar tendinopathy raises some concerns about potential biases stemming from the randomisation process. While randomisation was stated to have occurred, no details are provided regarding the specific methods used, hindering adequate assessment of this key domain. However, the study demonstrated methodological rigor across several other bias domains. Interventions were delivered according to pre-defined protocols with no reported deviations. Completeness of outcome data was excellent, with no attrition. Outcome assessments were performed consistently by the same experienced evaluator using validated, standardised instruments and testing protocols, guarding against detection biases. All pre-specified outcomes were transparently reported, showing no selective reporting bias. Despite the randomisation procedure lacking clarity, the trial exhibited robust methods that mitigated risks of performance, attrition, detection, and reporting biases. The authors' adherence to rigorous protocols for intervention delivery, data collection, outcome measurement, and transparent reporting enhances confidence in the overall internal validity of the findings. While randomization details are lacking, other key bias protections were seemingly adequate based on the published report.[33]

The strengths observed in the study conducted by Fogli M et al. (2017) included clearly stated objectives, well-described eligibility criteria, and the utilisation of pre-specified, valid, and reliable outcome measures. However, several notable weaknesses were identified. These encompassed limitations such as a small sample size, which could potentially compromise the study's statistical power and generalisability. Furthermore, the absence of randomisation raises concerns regarding potential biases in participant selection and treatment allocation. Additionally, the lack of clarity regarding blinding procedures introduces uncertainty regarding the reliability of outcome assessment.[34]

The evaluation of the study conducted by Frizziero A et al. (2019) highlights both strengths and weaknesses in its methodology. Noteworthy strengths include the clear articulation of objectives, well-described eligibility criteria, and the representation of participants. Additionally, the utilisation of pre-specified, valid, and reliable outcome measures enhances the credibility of the study's findings. However, significant limitations are evident, including a small sample size, which may compromise the study's statistical power and generalisability. The absence of blinding procedures raises concerns regarding potential biases in outcome assessment, potentially affecting the validity of the reported results. Furthermore, the absence of control subjects limits the ability to compare the intervention's effectiveness against alternative treatments or placebo.[35]

The appraisal of the study by Kumai T et al. (2014) highlights several methodological weaknesses. While the study's objectives are clearly stated, and eligibility criteria are adequately described, concerns arise regarding participant representation and the enrolment of all eligible participants. Furthermore, the study's small sample size undermines confidence in its findings, as it may lack the power to detect meaningful effects and limits the generalisability of the results. The absence of blinding procedures and statistical methods to account for pre/post changes further diminishes the study's quality, potentially introducing biases and confounding factors into the reported outcomes.[36]

Knee/patellar chondropathy

The evaluation of the study conducted by Astur DC et al. (2019) presents a mixed methodological profile. On one hand, the study exhibits strengths such as clear research questions and the utilisation of an appropriate study design, namely a randomised controlled trial. The description of randomisation methods adds to the study's methodological robustness, ensuring a more rigorous approach to participant allocation. Additionally, the reported blinding of outcome assessors enhances the reliability of the study's findings, minimizing potential biases in outcome assessment. However, despite these strengths, notable weaknesses are identified within the study's methodology. While the baseline characteristics between groups are reported to be similar, the absence of sample size justification or power calculation raises concerns regarding the adequacy of the study's statistical power to detect meaningful effects. Furthermore, the lack of reporting on effect sizes with precision estimates limits the interpretability and generalisability of the findings, hindering the ability to assess the clinical significance of the intervention's effects accurately. Moreover, although the study demonstrates a high follow-up rate with no reported dropouts, the absence of sample size justification or power calculation underscores a critical gap in the study's methodological rigor. Without adequate justification for sample size, there is an increased risk of Type II error, potentially overlooking clinically meaningful effects due to insufficient statistical power.[37]

Knee patellofemoral syndrome

The study by Hamawandi SA et al. (2021) demonstrates several strengths, including clear research questions, utilisation of a Randomised Controlled Trial (RCT) design, reporting of randomisation methods and the description of double-blinding. They are overall enhancing the methodological robustness of the study, minimising potential biases in participant allocation and outcome assessment. However, despite these strengths, several notable weaknesses are apparent within the study's methodology. While the baseline characteristics between groups are reported to be similar, the lack of justification for sample size raises concerns regarding the study's statistical power to detect meaningful effects. The absence of a clear rationale for sample size determination leaves the study susceptible to Type II error, potentially overlooking important treatment effects due to insufficient statistical power. Although the study utilises valid outcome measures such as the Visual Analog Scale (VAS) and the Kujala score, the precision of treatment effects is not reported. The absence of reporting on the precision of treatment

effects limits the interpretability and generalisability of the findings, hindering the ability to assess the clinical significance of the intervention accurately. Despite these methodological limitations, the study by Hamawandi SA et al. (2021) demonstrates a low overall risk of bias, indicating a certain level of methodological rigor. The absence of loss to follow-up further strengthens the reliability of the study's findings.[38]

Knee meniscus/ligament

The systematic review conducted by Mao B et al. (2023) performed a comprehensive literature search across major databases, indicating a thorough effort to identify relevant studies and minimise potential publication bias. The clear description of inclusion and exclusion criteria enhances the transparency and replicability of the study selection process, providing readers with insight into the criteria used for study inclusion. The Cochrane risk of bias tool to assess the methodological quality of included RCTs. The differentiation between RCTs with low and high risk of bias provides readers with valuable information regarding the quality of evidence underpinning the systematic review's conclusions. Moreover, the appropriate use of meta-analysis and the assessment of heterogeneity contribute to the robustness of the study's findings, allowing for the synthesis of data across multiple studies while considering potential variability between them. Despite these strengths, certain limitations are evident within the systematic review's methodology. The moderate risk of publication bias for some outcomes, such as Lysholm scores, warrants cautious interpretation of the findings, as the presence of publication bias may affect the reliability and generalisability of the synthesised evidence. Nonetheless, the overall low risk of bias for publication suggests that Mao B et al. (2023) employed rigorous methods to minimise biases in the identification and inclusion of studies, enhancing the credibility of their systematic review.[39]

Meanwhile, the systematic review conducted by Tripathy SK et al. (2022) demonstrates a thorough literature search across major databases, indicating a comprehensive effort to identify relevant studies and minimise potential bias in study selection. The clear description of inclusion and exclusion criteria further enhances transparency, providing readers with insight into the criteria used to determine study eligibility. Moreover, Tripathy SK et al. (2022) employed appropriate tools to assess the risk of bias in included studies. Utilising the Cochrane risk of bias tool for RCTs and the Newcastle-Ottawa scale for cohort studies allows for a systematic evaluation of the methodological quality of individual studies. Additionally, the systematic review appropriately pooled data from included studies and assessed measures of heterogeneity, allowing for the synthesis of data across multiple studies while considering potential variability between them.[40] However, it is worth noting that the systematic review did not assess publication bias unlike Mao B et al. (2023). While this may limit the ability to fully evaluate the potential impact of bias on the systematic review's findings, the overall low risk of bias for publication suggests that Tripathy SK et al. (2022) employed rigorous methods to minimise biases in study selection and inclusion.

(b) Ankle

Ankle tendinopathies

All RCTs for ankle tendinopathies were rated to have an overall low risk of bias as shown in **Figure 4.1**. The method of randomisation was stated while random sequence generation and allocation concealment were performed adequately. Outcomes were analysed using intention to treat analysis while selective reporting was considered to have a low risk of bias as all pre-specified outcomes were reported and analysed.

Three studies were included in this assessment and were summarised in **Figure 4.2**. The three Non-RCT studies had high risk of bias due to lack of control group and blinding of outcomes. GRADE quality of evidence was low for pain and function outcomes and very low for patient-reported improvement due to study limitations, inconsistency and imprecision. The Gorelick L et al. 2015 study is a non-randomized controlled trial comparing three parallel groups - hyaluronic acid injection, corticosteroid injection, and conservative treatment.[43] Although it was not a pure pre-post study with a single group and no control, the appropriate quality appraisal checklist for this type of quasi-experimental study design is the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group. The reasons to use this checklist include the groups were not randomised, thus, it is still considered an observational pre-post study design. The JBI checklist for Quasi-Experimental Studies is intended for studies using techniques like regression discontinuity, interrupted time series, or difference-in-differences analysis. These advanced techniques were not used in the Gorelick study. The JBI checklist also focuses on questions related to controlling for confounding and minimizing bias that are not relevant for a simple pre-post observational study like Gorelick L et al. The NIH Quality Assessment Tool for Pre-Post Studies with No Control better captures the key domains for critically appraising the methodological quality and risk of bias in a non-randomised comparative study like Gorelick L et al.

6.1 EFFICACY / EFFECTIVENESS

6.1.1 Knee

(a) Knee/patellar tendinopathy

Study by Kaux et al. (2019) found that both platelet-rich plasma (PRP) injections and hyaluronic acid (HA) injections were effective in alleviating symptoms of proximal patellar tendinopathy over a 3-month follow-up period. Patients in both treatment groups experienced significant improvements in pain levels assessed by the VAS scale ($p<0.01$), pressure algometry scores ($p<0.01$), and patient-reported outcome measures like the IKDC ($p<0.01$) and VISA-P questionnaires ($p<0.01$). However, only the PRP injection group showed a significant increase in quadriceps muscle strength during isokinetic testing at 3 months post-injection for the concentric 60°/s contraction mode (167.11 ± 49.12 Nm at baseline vs 159.38 ± 46.42 Nm at 3 months, $p=0.01$). In the HA injection group, while VAS pain levels decreased significantly during isokinetic strength testing for all contraction modes after 3 months (e.g. VAS for eccentric 30°/s went from 5.66 ± 2.46 at baseline to 3.66 ± 3.13 at 3 months, $p<0.05$), no overall improvement in quadriceps peak torque was observed compared to baseline. The study reported 77.8% of patients were responders (>50% pain reduction) in the PRP group and 73.3% in the HA group.

Regarding safety, no major adverse events were reported with either PRP or HA injections in this study. Both treatments were described as being well-tolerated by patients. The authors did not provide any specific numerical safety data such as rates of post-injection pain, swelling or other local complications. In summary, while both treatments significantly improved pain and function, PRP provided an additional statistically significant benefit of increasing quadriceps strength by 8-10 Nm over baseline in the involved limb based on isokinetic testing.[33]

Fogli M et al. conducted an open-label trial in 2017, focusing on 71 patients (26 with patellar tendons) who received three weekly IAHA injections. The study aimed to assess the effects of this intervention and its impact on VAS pain scores after 56 days. The outcomes revealed a substantial mean decrease of 6.16 cm in VAS pain scores, signifying a significant reduction ($p<0.001$). However, despite clear objectives and descriptions of the intervention, the study presented a high risk of bias due to its lack of a control group and blinding. While the outcome measures were pre-specified and the statistical methods adequately examined pre/post changes, the absence of a control group and blinding aspects limits the study's reliability and certainty in determining the true effectiveness of IAHA injections for patellar tendinopathy.[34]

Frizziero A et al. conducted a pre-post study in 2019 involving 35 patients who received three weekly IAHA injections. The study aimed to assess the impact of this treatment on patients' outcomes at the 90-day mark. Notably, the outcomes revealed a significant mean increase of 19.25 points on the VISA-P score (p=0.0022) and a mean decrease of 4.75 points on the NRS-11 pain score (p=0.0040). However, despite addressing a relevant issue and accounting for all patients involved, the study's design lacked randomisation and a control group, indicating a high risk of bias. While the observed effects appeared substantial, the absence of a control comparator limits the certainty of attributing these changes solely to the IAHA treatment, thereby making the true magnitude of its benefits uncertain.[35]

Kumai T et al. conducted a study in 2014 which, despite addressing a relevant issue, was deemed as an uncontrolled pre-post study, lacking randomised patient assignments. The study, though accounting for all patients involved, presents a high risk of bias. It reported noteworthy findings, indicating a mean pain score improvement of 2.01 cm (95% CI: -3.26 to -0.77) on the VAS scale after a single IAHA injection at the one-week follow-up (*p-value = 0.004*). Additionally, half of the participants (n=7) experienced a substantial improvement of at least 2 cm in VAS pain scores, alongside enhancements in local symptoms such as pain, tenderness, and provoked pain. However, due to the absence of a control group, the study's reliability in quantifying the benefits of IAHA remains uncertain, limiting the ability to ascertain the true magnitude of its effects.[36]

(b) Knee/patellar chondropathy

Astur DC et al. (2019) conducted an RCT evaluating the efficacy of intraarticular hyaluronic acid (IAHA + physical therapy vs physical therapy) for treating patellar chondropathy. The study was well-designed, with clear research questions, descriptions of randomisation methods, and blinding of outcome assessors. The groups showed similar baseline characteristics, and validated outcome measures such as Kujala, VAS pain and Lysholm score were appropriately utilised. However, the study lacked sample size justification, power calculation, and precision estimates for effect sizes. Despite this, IAHA demonstrated promising results in pain relief, showing lower VAS pain scores at 3 and 6 months compared to alternative treatments ($p<0.05$). This suggests the potential superiority of IAHA for short-term pain relief in patellar chondropathy. Additionally, IAHA displayed higher Lysholm scores at 3 and 6 months ($p<0.05$), indicating improved functionality, thus highlighting its potential benefits in enhancing functional outcomes for individuals with patellar chondropathy.[37]

(c) Knee patellofemoral syndrome

In the study by Hamawandi SA et al. (2021), which employed a randomised controlled trial design, the research questions were clearly delineated, and the randomisation

methods, as well as double-blinding procedures, were reported. Baseline characteristics between groups were similar, and validated outcome measures such as VAS and Kujala score were appropriately utilised. The study also applied suitable statistical tests and reported no loss to follow-up. However, the sample size was not justified, and the precision of treatment effects was not reported. Nonetheless, the findings indicated promising results for IAHA in treating the subjects. The IAHA group exhibited significantly lower VAS pain scores at the 6-month mark compared to the control group (p=0.035), suggesting its efficacy in providing pain relief over the short term. Moreover, the IAHA group demonstrated significantly higher Kujala function scores over a 2-year period in contrast to the controls, highlighting its potential effectiveness in enhancing functional outcomes for individuals undergoing IAHA treatment.[38]

(d) Knee meniscus/ligament

Mao B et al. (2023) primarily concentrated on individuals with knee ACL/meniscus injuries. Their meta-analysis, which encompassed seven randomised controlled trials (n=951), revealed no significant difference in VAS pain scores between groups treated with IAHA and control groups, both at less than 6 months (SMD 0.01, 95% CI -0.17 to 0.20, p=0.90) and beyond 6 months (SMD -0.07, 95% CI -0.32 to 0.17, p=0.55). Additionally, their findings indicated that IAHA did not exhibit any discernible advantage in terms of functional recovery. The pooled analysis of WOMAC scores from six RCTs showed no statistically significant differences (SMD -2.92, 95% CI -7.54 to 1.71, p=0.25). The review of available evidence suggests that IAHA injection after knee arthroscopic surgery does not contribute to improvements in pain relief and functional recovery, compared to other management approaches after knee arthroscopic surgery. And there was no difference between the effect of high- and low- molecular HA applied following knee arthroscopic surgery. Based on the available evidence, the application of HA injection after arthroscopic knee surgery is not recommended.[39]

Tripathy SK et al. (2022) concentrated on individuals who underwent ACL reconstruction surgery. Their analysis, combining data from three RCTs and one cohort study (n=303), revealed no significant divergence in VAS pain scores between groups treated with IAHA and control groups. This was observed across various postoperative periods, specifically at 2 weeks, 4-6 weeks, and 8-12 weeks (p>0.05 for all). Moreover, Tripathy SK et al. observed no enhancements in functional outcomes as assessed by Lysholm and IKDC scores (p>0.05). Although the individual study demonstrated a short-term positive response regarding pain control and swelling reduction, the pooled analysis did not find any clinical benefit of IAHA injection following ACLR surgery.[40]

Table 5 provides an overview of the results obtained from the included studies above.

Table 5: Outcomes of included studies

Author / Study design	No. of studies / No. of patients	Pain		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
KNEE/PATELLAR TENDINOPATHY					
Kaux et al. 2019 RCT	33 patients	Over 6 weeks and 12 weeks: Fourteen out of 18 subjects (77, 8%) in the PRP group and 11 out of 15 subjects (73, 3%) in the HA group were responders to the treatments (decrease of pain >50%). VAS ($p<0.01$), algometric scores ($p<0.01$), IKDC scores ($p<0.01$) and VISA-P ($p<0.01$) showed a considerable improvement in the two groups with time. Correlations showed that there was a significant negative association between VAS and strength in C60 ($r =-0.66$, $p =0.0030$), C240 ($r =-0.56$, $p = 0.016$), and E30 ($rs =-0.66$, $p =0.0030$) only for the PRP group but these associations were moderate There was no significant association between the VAS score and strength for the HA group ($p > 0.05$).			
Frizziero et al. (2019) A prospective multicentric clinical trial	35 patients altogether with 8 patients of patellar tendinopathy	**NRS-11 for pain** Score significantly decreased in subjects with patellar tendinopathy during the study (p=0.004).	-	**VISA-P** Followed-up at 14, 45 and 90 days after the procedure showed significant improvement in VISA-P score (19.25±11.61; 95% CI: 9.54 to 28.96; p=0.0022)	-
Fogli et al. (2017) Prospective Open-label single centre clinical study	62 patients altogether in which 11 patients (15.5%) were among patellar tendons	**VAS (pain)** mean VAS value V1 = 7.59 cm ± 0.97 (baseline) (Day 1) V2 = 5.32 cm ±1.60 (Day 7); V3 = 3.95 cm±1.64 (Day 14); V4 = 2.50 cm±2.16 (p<0.001) (Day 56)	-	**Mean sagittal thickness of patellar tendon** V1 = 7.09 mm ±1.65 (baseline) (Day 1) V3 = 6.55 mm ±1.36 (Day 14) V4 = 6.16 mm (±1.58) (Day 56)	-
Kumai et al. (2014) / Prospective Open-label single centre clinical study	61 patients altogether in which 14 patients were among patellar tendons.	**VAS (pain) 1 week after treatment** Pre = 4.00 ± 2.18 (95% CI: 2.74 to 5.26) Post = 1.99 ± 1.43 (95% CI: 1.16 to 2.81) Amount of change, cm -2.01 ± 2.16 (95% CI: -3.26 to - 0.77) Percentage of change % -35.6 ± 52.1 P-value = 0.004	-	-	-
KNEE/PATELLAR CHONDROPATHY					
Astur et al. (2019) / RCT	70 patients	**Kujala score** **3 months** [PE + HA] 79.3 ± 13 (42-100) vs [PE] 69.2 ± 11.5 (40-90) (p=0.001) **VAS score** **3 months** [PE + HA] 2.8 ± 2.3 (0-7) vs [PE] 3.8 ± 1.3 (2-6) (p=0.02)	**Kujala score** **6 months** [PE + HA] 79.7 ± 15 (43-100) vs [PE] 71.3 ± 10.8 (50-91) (p=0.01) **VAS score** **6 months** [PE + HA] 2.7 ± 2.1 (0-8) vs [PE] 3.5 ± 0.9 (2-6) (p=0.01)	**Lysholm scale** **3 months** [PE + HA] 82.6 ± 14.7 (36-100) vs [PE] 74.3 ± 15.3 (43-93) (p=0.02)	**Lysholm scale** **6 months** [PE + HA] 81.5 ± 16.7 (41-100) vs [PE] 75.9 ± 12.7 (47-95) (p=0.02)

Author / Study design	No. of studies / No. of patients	Pain		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
KNEE PATELLOFEMORAL SYNDROME					
Hamawandi et al. (2021) / RCT	90 patients	**VAS score** **Group A** 3 months postoperative: 25.02 6 months postoperative: 29.83 All p-value <0.001 **Group B** 3 months postoperative: 23.21 6 months postoperative: 23.93 All p-value <0.001	**VAS score** **Group A** 1 year postoperative: 43.09 2 years postoperative: 50.99 All p-value <0.001 **Group B** 1 year postoperative: 32.86 2 years postoperative: 45.89 All p-value <0.001	**Kujala score** **Group A – Paired t-test** 3 months postoperative: − 36.57 6 months postoperative: −42.57 All p-value <0.001 **Group B – Paired t-test** 3 months postoperative: −34.63 6 months postoperative: − 37.46 All p-value <0.001	**Kujala score** **Group A – Paired t-test** 1 year postoperative: −46.96 2 years postoperative: − 48.18 All p-value <0.001 **Group B – Paired t-test** 1 year postoperative: − 44.39 2 years postoperative: −44.99 All p-value <0.001
KNEE MENISCUS/LIGAMENT					
Mao B et al. (2023) / Systematic review and meta-analysis	15 RCTs were included for qualitative synthesis: 7 RCTs included for meta-analysis.	**VAS-scoring** **Follow-up time** The analysis showed no significant difference between the HA and control groups within post-operative 6-month time point (SMD 0.01; 95% CI - 0.17 to 0.20; P = 0.90) Moderate heterogeneity (I^2 = 26%), and **ACL reconstruction** There was no significant difference between the HA and control groups in ACL reconstruction (SMD-- 0.06; 95% CI -0.44 to 0.32; P = 0.77) Heterogenity was 27%.	**VAS-scoring** The analysis showed no significant difference between the HA and control groups over the postoperative 6-month time point (SMD -0.07; 95% CI 0.32 to 0.17; P = 0.55), no heterogeneity (I^2 = 0%).	-	**WOMAC Total score** There was no significant difference between the HA and control groups at the time point less than 12-month follow-up (MD - 1.36; 95% CI - 4.31 to 1.59; P = 0.37) and also for time point longer than 12- month follow-up (MD - 22.37; 95% CI - 57.95 to 13.20; P = 0.22). In overall, there was no significant difference either (MD - 2.92; 95% CI -7.54 to 1.71; P = 0.25). **Heterogenity** <12 month = 6% >12 month = 74% Overall = 50% **Other Functional Scales** 5 studies display result on Lysholm score which showed a trend favouring HA group but did not show any differences (MD 6.01; 95% CI - 1.74 to 13.75; P = 0.13). The heterogeneity was 86%. IKDC and Tegner also showed no significant difference but had opposite trend compared to Lysholm score. Heterogeneity for IKDC and Tegner are (I^2 = 55% and 0%, respectively).

Author / Study design	No. of studies / No. of patients	Pain		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
Tripathy et al. (2022) / Systematic review	4 studies in which 3 were RCT and 1 cohort study.	**Primary objective: Pain (VAS)** No significant difference between the HA and control groups after ACLR at 2-week, 4-6 weeks & 8-12 weeks (p>0.05).	-	**Secondary objective:** The knee swelling was significantly less in the HA group at two weeks (MD -7.85, 95% CI: [-15.03, 0.68], p = 0.03, I2 = 0%), but no such difference was noted after 4-6weeks and 8-12 weeks. The functional outcome score was not significantly different between the groups (SMD 0.00, 95% CI: 0.38 to 0.38, p = 0.99, I^2. 0%).	-
VAS: Visual Analogue Scale, NRS: Numerical Rating Scale: VISA-P: Victorian Institute of Sport Assessment-Patella, WOMAC: Western Ontario and McMaster Universities Arthritis Index					

6.1.2 Ankle

Ankle tendinopathies (including ligament and tendon injuries)

The study by Kumai T et al. (2018) found that patients receiving high molecular weight hyaluronic acid (HMW-HA) had a significantly greater reduction in pain scores on the visual analogue scale (VAS) from baseline to 5 weeks compared to the control group in 168 patients with plantar fasciopathy. Specifically, the HMW-HA group had a mean decrease of 3.3 cm on the VAS, while the control group had a mean decrease of 2.4 cm. The low molecular weight HA (LMW-HA) group also had a greater decrease in VAS pain scores (2.6 cm) compared to control, but this difference was not statistically significant. This indicates that HMW-HA injections resulted in significantly improved pain relief compared to placebo injections in patients with plantar fasciopathy over a 5-week period.[41]

Lynen N et al (2016) conducted a randomised controlled trial comparing two ultrasound-guided IAHA injections (40mg hyaluronate + 10mg mannitol) versus three sessions of extracorporeal shockwave therapy (ESWT) in 59 patients with midportion Achilles tendinopathy. Follow-up was 6 months. The IAHA group showed significantly greater improvement in pain scores (-88% versus -52% change at 3 months) and function (VISA-A scores) compared to ESWT.[42]

Gorelick L et al (2015) performed a non-randomised controlled study comparing a single IAHA injection to corticosteroid injection or conservative therapy in 56 patients with insertional Achilles tendinopathy over 6 months. The IAHA group had significantly greater increases in Foot and Ankle Disability Index (FADI) scores (65 points for

hyaluronic acid versus 55 points for corticosteroid and 49 points for conservative) and decreases in pain scores compared to control groups.[43]

Fogli M et al (2017) performed an open-label pre-post study of three weekly IAHA injections in 34 patients with Achilles tendinopathy. At 90-day follow-up, there were significant improvements in Victorian Institute of Sport Assessment-Achilles (VISA-A) scores (23-point increase), pain scores (4.5-point decrease on NRS) and ultrasound tendon parameters.[34] Frizziero A et al (2019) conducted an open-label pre-post study of three weekly IAHA injections in 26 patients with Achilles tendinopathy. At 90-day follow-up, VISA-A scores showed significant increases from baseline (23- and 19-point increases, respectively) as well as reduction in NSR-11 score suggesting improvement in pain. However, the study is lack of control group, had small sample size and short follow up duration.[35] Table 6 presents a summary of the findings from the included studies.

Table 6: Outcomes of included studies for ankle tendinopathies

Author / Study design	No. of studies (no. of patients)	Pain		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
Kumai T et al. (2018) RCT	n=168 plantar fasciopathy	**VAS pain score:** HMW-HA injections (−3.3±0.3 cm) resulted in significantly improved pain relief (P=0.029) compared to placebo injections (−2.4±0.3 cm) in patients with plantar fasciopathy over a 5 week period.	-	-	-
Lynen N et al. (2017) RCT	n=59 Achilles tendinopathy	**3 months follow up** The HA group had significantly greater percent reduction in **pain scores** compared to ESWT at 3 months (-88.2% vs -51.6%, p=0.003).	**6 months follow up** The HA group still showed significantly greater pain reduction (-94.9% vs. -66.4%, p = 0.0018).	**3 months follow up** The HA group had significantly greater improvement in **VISA-A scores** (73 vs 47.5 p=0.0056), clinical parameters, and clinical global impression (CGI) scores compared to ESWT.	**6 months follow up** The HA group showed significantly higher VISA-A scores (75 vs 52 p = 0.0064).
Gorelick L et al. (2015)	56 patients with insertional Achilles tendinopathy		**6 months follow up** **VAS pain score:** HA group (-4.88 points) vs corticosteroid (-3.95 points) vs conservative treatment (-2.68 points) (ANOVA, p < 0.05) HA vs conservative treatment = 2.2 points, indicating a medium to large effect size favouring HA		**6 months follow up** **FADI score:** HA (64.77 points) vs corticosteroid (55.39 points) vs conservative treatment (48.96 points) (ANOVA, p < 0.05) Effect size: HA vs conservative treatment = 15.81 points, suggesting a large effect size in favour of HA

Author / Study design	No. of studies (no. of patients)	Pain		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
Fogli M et al. (2017) Cohort, open-label clinical trial	34 patients with Achilles tendinopathy	Significant reduction in VAS (p<0.001) from baseline (-6.16 ± 0.45 cm).			
Frizziero A et al. (2019) / A prospective multicentric clinical trial	26 patients Achilles tendinopathy	**NRS-11 for pain:** Score significantly decreased in subjects with patellar tendinopathy during the study (p=0.004).	-	**VISA-A score:** Followed-up at 14, 45 and 90 days after the procedure showed significant improvement in VISA-A score Baseline: 44.88 ± 17.37 Day 90: 67.17 ± 22.66 Mean change: 23.22 ± 23.17 (95% CI: 13.20 to 33.24; p=0.0001)	-

Ha: hyaluronic acid, VAS: Visual Analogue scale, NRS: numerical rating scale, VISA-A: Victorian Institute of Sport Assessment-Achilles, FADI: Foot and Ankle Disability Index

PART III : OSTEOARTHRITIS OF THE SHOULDER, HIP, KNEE AND ANKLE

7.0 RESULTS

Search results

A total of **1,485** records were identified through the Ovid interface and PubMed, with an additional **34** records found from other sources or references within the retrieved articles. Following the removal of **221** duplicate records, **1,298** potentially relevant titles were screened using the inclusion and exclusion criteria. Subsequently, **76** abstracts were selected for full-text review due to their potentially relevance. Following a comprehensive assessments, **18** full-text articles were included into our analysis. These articles covered various aspects of osteoarthritis, with **four focusing on shoulder OA, six on hip OA, five on knee OA, and three on ankle OA.** The included studies comprised two systematic review with network meta-analysis, 11 systematic review with meta-analysis, three systematic reviews, and two RCTs. The studies were conducted mainly in the United States (four studies), China (three studies), Taiwan, the Netherlands, Brazil, Canada, Italy, Spain, Japan, and Pakistan. An overview of the search is illustrated in **Figure 5**.

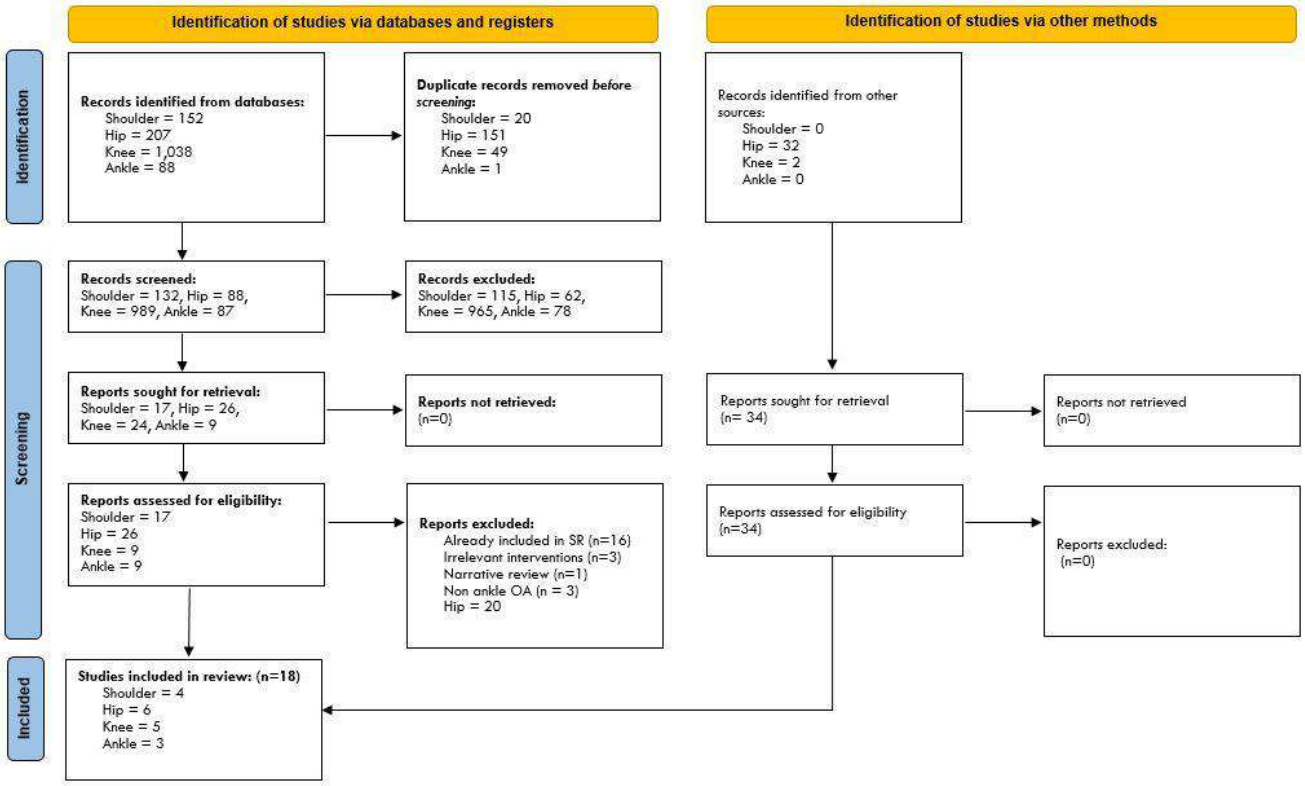

Figure 5: PRISMA 2020 flow diagram of retrieval of articles used in the results for osteoarthritis of the shoulder, hip, knee and ankle

Quality assessment of the studies

The risks of bias in the included studies were assessed using the domain-based evaluation. Tools that are being used to assess the risk of bias are adapted from the ROBIS, and the Cochrane Risk of Bias (RoB 2.0) checklists. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

x	High
-	Unclear
+	Low
?	No information

While the majority of the studies exhibited a low risk of bias, there were notable concerns regarding a high risk of bias in studies focusing on osteoarthritis of the shoulder, hip, and ankle. Furthermore, many of the studies included in this technology review had small sample sizes, potentially limiting their ability to adequately represent the broader population of interest. The results of risk of bias of included studies are summarised in **Figure 5.1 to 5.2**.

			Risk of bias				
			D1	D2	D3	D4	Conclusion
Study	Shoulder	Familiari F et al.[44]	x	+	+	+	x
		Zhang B et al.[45]	+	+	+	+	+
	Hip	Belk JW et al.[48]	+	+	+	-	-
		Sambe HG et al.[49]	+	+	+	+	+
		Ali SE et al.[50]	+	+	+	+	+
		Medina-Porqueres I et al.[51]	+	+	+	x	x
		Wu YZ et al.[52]	+	+	+	x	x
		Leite VF et al.[53]	+	+	+	+	+
	Knee	Xue Y et al.[54]	+	+	+	+	+
		Lin X et al.[55]	+	+	+	+	+
		Belk JW et al.[56]	+	+	+	+	+
		Mojica ES et al.[57]	+	+	+	+	+
		Tan J et al.[58]	+	+	+	+	+
	Ankle	Paget LD et al.[59]	+	+	+	-	-
		Witteveen AG et al.[60]	+	+	+	+	+
		Chang KV et al.[61]	+	+	+	x	x

D1: Concerns regarding specification of study eligibility criteria.
D2: Concerns regarding methods used to identify and/or select studies.
D3: Concerns regarding methods used to collect data and appraise studies.
D4: Concerns regarding the synthesis and findings.
CONCLUSION: Risk of bias in the review.

Judgement

x	High
-	Unclear
+	Low
?	No information

Figure 5.1: Risk of bias assessment for systematic review using ROBIS

Risk of bias assessment for included RCT

			Risk of bias					
			D1	D2	D3	D4	D5	Overall
Study	Shoulder	Kubo T et al.[46]	+	+	+	+	+	+
		Tortato S et al.[47]	+	+	+	x	+	x

D1: Bias arising from the randomisation process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement

x	High
-	Some concerns
+	Low
?	No information

Figure 5.2: Risk of bias assessment for RCT using RoB 2.0

(a) Shoulder osteoarthritis

Familiari F et al. (2023) was rated to have an overall high risk of bias. Electronic searches were performed using PubMed, Scopus, and Web of Science for publications from 2007 to 2022, and adhered to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Cochrane guidelines. The review included diverse study designs among its 15 reports, comprising seven RCTs, five single-arm open-label trials, one retrospective single-arm interventional study, one retrospective cohort, and a case series. The risk of bias assessment utilised the Physiotherapy Evidence Database (PEDRO) scale, and statistical analyses were performed using R 3.5.0 (R Foundation) and Review Manager (RevMan) software, Version 5.3.[44]

In contrast, Zhang et al. (2019) was rated to have a low risk of bias. Systematic searches were conducted in three databases up to January 16, 2018, including articles online ahead of print, and abided to PRISMA and Cochrane guidelines. The quality assessment involved the Methodological Index for Non-Randomized Studies (MINORS) tool for non-randomised studies and the Cochrane Risk-of-Bias Tool for RCTs. The Grading of Recommendations Assessment, Development and Education (GRADE) approach assessed evidence quality, and statistical analyses used RevMan 5.2 software. Both studies included analyses of statistical heterogeneity and sensitivity.[45]

Kubo T et al. (2022) have a generally low risk of bias. They ensure adequate random sequence generation and allocation concealment, with both patients and investigating personnel blinded during treatment and evaluation. Additionally, baseline comparability between the intervention and control groups was consistently maintained in all groups. Assessments were conducted at

similar time points, with loss to follow-up of 10 patients (3.5%). The study selective reporting demonstrated minimal bias, as all pre-specified outcomes were reported and analysed.[46]

However, Tortato S et al. (2022) have a higher risk of bias. While participants underwent randomisation, the process was not thoroughly described. Only participants were blinded to the intervention, while the attending physicians were unblinded during procedures and evaluation. Baseline comparability was ensured between groups. All participants received equal treatment and underwent assessments at specified post-treatment intervals. However, there were concerns regarding results reporting, with a proportion of seven participants (9%) were excluded during follow-up without clear reasons provided. Despite this, all pre-specified outcomes were reported and analysed.[47]

(b) Hip osteoarthritis

The assessment of the included studies follows a rigorous evaluation across key domains, shedding light on the robustness and reliability of the evidence presented.

Belk JW et al. (2022) demonstrated a low risk in terms of paper selection, relevance, and quality assessment. However, the risk of bias related to heterogeneity remains unclear. The study acknowledges the presence of clinical and statistical heterogeneity across studies but lacks sufficient power for a comprehensive analysis, contributing to the uncertainty in risk assessment.[48]

Sambe HG et al. (2023) exhibited consistently low risks across all domains, showcasing a well-structured and methodologically sound study. The inclusion criteria, quality assessment, and absence of heterogeneity concerns contribute to the overall credibility of the findings.[49] Ali et al. (2021) aligns with the trend of low risks, emphasising a careful selection of relevant studies and a meticulous assessment of their quality. The study adds to the robustness of the evidence base with its methodological rigor and absence of notable biases.[50]

Medina-Porqueres I et al. (2021) introduced a nuanced perspective, marked by low risks in paper selection, relevance, and quality assessment. However, the study grapples with high clinical and statistical heterogeneity, raising concerns about the generalisability of the findings and contributing to an elevated overall risk of bias.[51] Wu YZ et al. (2021) exhibits commendable methodological rigor in paper selection and quality assessment, positioning it as a valuable contribution. Despite this, the study faces challenges with high heterogeneity, prompting the classification of an elevated overall risk of bias. The acknowledged high heterogeneity signals potential differences among the studies, casting a shadow on the robustness of the synthesised results.[52]

In summary, while the majority of the studies maintain a low risk across domains, those with high heterogeneity, such as Medina-Porqueres I et al. (2021) and Wu YZ et al. (2021), underscore the importance of cautious interpretation and consideration of potential biases in

the overall assessment of intraarticular hyaluronic acid injection effectiveness for hip osteoarthritis.

Methods

Ali SE et al. (2021) conducted a systematic review and meta-analysis with the aim of evaluating the efficacy of high molecular weight HA intra-articular injection for the hip joint. They scrutinized randomised trials found through searches in PubMed, Google Scholar, and the Cochrane Database. The inclusion criteria specified patients with hip OA, excluding those with other arthritic conditions. The review, while of moderate overall quality, raised concerns regarding randomisation and blinding processes.[50]

Sambe HG et al. (2023) pursued a similar path, engaging in a systematic review and meta-analysis comparing IAHA to PRP for hip OA. The analysis, encompassing seven RCTs, delved into outcomes related to pain (WOMAC and VAS scales) and function (Harris Hip Score). The overall quality of the systematic review was appraised as moderate, with similar concerns about randomisation and blinding processes.[49]

Belk JW et al. (2022) opted for a systematic review and meta-analysis focusing on six RCTs, comparing IAHA injections to PRP injections for hip OA. Their comprehensive evaluation considered outcomes related to pain, function, complications, and hip survivorship. The quality appraisal involved the Cochrane Risk of Bias Tool, and Modified Coleman Methodology Scores were calculated to evaluate study quality.[48]

Medina-Porqueres I et al. (2021) pursued a systematic review and meta-analysis involving four trials, with a focus on adults with symptomatic hip OA in Italy. Their outcomes measured spanned pain (VAS, WOMAC), functionality (HHS), growth factors concentration, adverse effects, and imaging evaluations. The methodologies applied ensured a thorough examination of the available evidence.[51]

Wu YZ et al. (2021) formulated a research question related to the efficacy and safety of hyaluronic acid (HA) of different molecular weights for the treatment of hip OA. Utilising three databases, they assessed studies using the Downs and Black checklist, classifying HA into different molecular weight categories. Statistical analyses were conducted using Review Manager (version 5.3), with subgrouping based on molecular weight classifications and follow-up time.[52]

(c) Knee osteoarthritis

Xue Y et al. (2023) and Lin X et al. (2022) both conducted a network meta-analysis with a low risk of bias. Xue Y et al. conducted a systematic searched using seven databases – four English databases (PubMed, EMBASE, Web of Science, and Cochrane Library) and three Chinese databases (China Biology Medicine disc, Wan-Fang, and China National Knowledge Infrastructure), up to December 2021, with predefined clinical question and inclusion criteria.

The review involved independent screening, extraction, and quality assessments by two reviewers, with discrepancies resolved by a third author. Risk of bias analysis was performed using Review Manager 5.4 software and network meta-analysis was conducted by STATA/MP 15.1. Surface Under the Cumulative Ranking Curve (SUCRA) was utilised for ranking treatment methods, and statistical heterogeneity and sensitivity analyses were included.[54]

Similarly, Lin X et al. (2022) achieved a low risk of bias. A systematic search was performed using PubMed, VIP, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), and Wan-Fang databases up to July 20, 2021. They also had predefined clinical question and inclusion criteria, involved independent screening, extraction, and quality assessments by two reviewer, and discrepancies resolved through consensus decisions with a third reviewer. The study adhered to the Cochrane Handbook for Systematic Evaluation of the Cochrane Collaboration Network (version 5.1.0) and NICE Reticulated Meta-analysis Reporting Specification. Treatment probabilities were evaluated using SUCRA, and statistical heterogeneity and sensitivity analyses were performed.[55]

Additionally, Belk JW et al. (2023), Mojica ES et al. (2022) and Tan J et al. (2020) were rated to have a low risk of bias. Belk JW et al. systematically searched PubMed, EMBASE and the Cochrane Library up to August 15, 2022, with predefined clinical question and inclusion criteria. This study was conducted according to the PRISMA guideline, study methodology quality utilised the Modified Coleman Methodology Score, and risk of bias (ROB) assessed using Cochrane Collaboration's ROB tool. Analyses were performed using a combination of RevMan 5.3, R version 4.2.2, and the Netmeta R package. Statistical heterogeneity and sensitivity analyses were included.[56]

Mojica ES et al. conducted a systematic search using Medline, EMBASE, and the Cochrane Library in September 2020, with predefined clinical question and inclusion criteria. Their review involved independent screening, extraction, and quality assessments by two reviewers, with disagreements resolved by a third author. Risk of bias analysis and methodological quality of evidence assessment were conducted following Cochrane guidelines, and the study was reported based on PRISMA guidelines. They also included reports on statistical heterogeneity and sensitivity analyses.[57]

Similarly, Tan J et al. (2020) conducted a systematic search using eight databases up to December 2019, without language restrictions, with predefined clinical questions and inclusion criteria. Independent screening, extraction, and quality assessments were performed by two reviewers, with consultations with two senior authors to resolve disagreements. Their methodological quality assessment followed a modification of the Cochrane evaluation tool, and the study was reported based on PRISMA guidelines. The Review Manager Database (RevMan version 5.3) was used to analyse the included studies. They also included reports on statistical heterogeneity and sensitivity analyses.[58]

(d) Ankle Osteoarthritis

The credibility of the findings in all included studies has been thoroughly investigated to explore the risk of bias across key domains.

Paget LD et al. (2023) conducted a systematic review with comprehensive search strategies, ensuring all relevant studies were included. However, despite low risk in the right type of paper selection and assessment quality of included studies, the overall quality of evidence was rated as very low for two interventions and moderate for one. Most included studies had a high risk of bias, leading to concerns about bias. The review appropriately concluded that additional high-quality RCTs are necessary to establish the efficacy and safety of IAHA for ankle OA. The low number of studies and participants, as well as heterogeneity, limit the possibility of performing subgroup analysis on the efficacy of interventions or a meta-analysis.[59]

Witteveen AG et al. (2015) score a low risk of bias in all domains, strengthening the overall credibility of the findings.[60] Chang Ke-Vin et al (2013) exhibit a high overall risk of bias due to a high risk of bias in domains such as quality assessment and heterogeneity. The authors failed to report the quality assessment of the included studies. The study also struggles with high heterogeneity (I^2 = 92.1%, P=0.000). In addition, more than half of the included studies did not possess a randomised controlled design, making them unclear in terms of risk of bias in methodology.[61]

In summary, only Witteveen AGH et al. (2015) demonstrated a low overall risk of bias. The studies that score high or unclear in overall risk of bias require a careful interpretation of potential bias in the findings. Each systematic review contributed valuable insights into the effectiveness of IAHA for ankle OA but faced methodological challenges. The presence of high heterogeneity and potential publication bias in some studies underscore the importance of transparent reporting and inclusion of unpublished data to enhance the reliability of findings. Additionally, concerns regarding bias in the included studies highlight the need for rigorous quality assessment and further high-quality RCTs to strengthen the evidence base for IAHA in ankle OA management. The assessment of the risk of bias is summarised in Figure 5.1.

Methods

Chang KV et al. (2013) conducted a systematic review and meta-analysis aimed at evaluating the effectiveness of IAHA injections for ankle OA, as well as exploring the effects of modified regimens of HA. Their search strategy encompassed PubMed, Scopus, and additional sources such as the Cochrane Collaboration Central Register of Controlled Clinical Trials and ClinicalTrials.gov. They included human clinical trials focusing on adult participants with confirmed ankle OA and symptoms lasting more than 6 months. Quality assessment was performed using the Jadad scale, with two reviewers independently evaluating the risk of bias in included studies. Data synthesis involved estimating effect sizes from pain scores and employing standardised mean differences to compare outcomes across studies and between different therapeutic approaches. The meta-analysis included 354 participants, predominantly

male (54.8%) with mean ages ranging from 45 to 60 years. Most studies recruited patients with ankle OA severity equalling or exceeding grade 2 in the Kellgren-Lawrence scale, with durations from symptom onset to study registration ranging from 2 to 5.3 years.[61]

Witteveen AG et al. (2015) conducted a systematic review assessing the benefits and harms of conservative treatments for ankle OA in adults. Their search strategy covered multiple databases including Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and others. Quality assessment was conducted using Cochrane's tool for assessing risk of bias, focusing on aspects such as allocation sequence generation, blinding, incomplete outcome data, and selective outcome reporting. The review included a total of 240 participants clinically diagnosed with ankle OA and confirmed radiographically, with follow-up periods ranging from 3 to 12 months. Different types of HA, dosage, and dosing schedules were utilised across the included trials, emphasising the heterogeneity in treatment regimens evaluated for ankle OA management.[60]

Paget LD et al. (2023) conducted a systematic review and meta-analysis to evaluate the effectiveness of intra-articular injections for ankle OA, including IAHA among other interventions such as PRP and botulinum toxin Type A (BoNT-A). Their search strategy included PubMed, Embase, Google Scholar, and the Cochrane Database, yielding seven relevant RCTs. Quality assessment was performed using Cochrane criteria, focusing on risk of bias indicators such as inconsistency, indirectness, imprecision, and publication bias. Data synthesis involved extracting relevant data from included studies, including participant characteristics, intervention details, outcome measures, and safety data. The meta-analysis included a total of 340 patients with ankle OA, with mean age of 52 ± 21 years and 35% being women. Different interventions, including HA, PRP, BoNT-A, and saline, were evaluated across various trials, with follow-up periods ranging from 3 to 12 months.[59]

Overall, these systematic reviews and meta-analyses utilised rigorous methodologies to evaluate the effectiveness of IAHA injections for ankle OA. They employed comprehensive search strategies, quality assessment tools, and data synthesis techniques to provide valuable insights into the efficacy and safety of IAHA treatment. However, limitations such as heterogeneity among studies, risk of bias, and quality of evidence should be carefully considered when interpreting the findings in the context of clinical practice and decision-making.

7.1 EFFICACY / EFFECTIVENESS

7.1.1 Glenohumeral/shoulder osteoarthritis

Familiari F et al. (2023) conducted a systematic review and meta-analysis to evaluate the current evidence on the efficacy of intra-articular hyaluronic acid (IA HA) in alleviating pain among patients with glenohumeral joint osteoarthritis (GH-OA). They conducted an electronic search across three databases for relevant studies published in the last 15 years, from 2007 to 2022. The inclusion criteria comprised randomised controlled trials investigating pain **post-hyaluronic acid infiltrations as a therapeutic intervention** for individuals diagnosed with shoulder osteoarthritis. A total of 15 articles were included and categorised into five main groups:

(1) HA injection from a single-arm open-label trials (seven studies);
(2) HA injections combined with physical therapy (PT) versus PT alone (three studies);
(3) HA versus corticosteroid injections (two studies);
(4) HA versus placebo control groups (two studies);
(5) HA versus platelet-rich plasma (PRP) (one study).

Among these studies, four reported the severity of osteoarthritis in the participants. Specifically, two studies included individuals with grade II or III osteoarthritis, one study enrolled participants with grade I, II or III, and another study focused on participants with grade II, III or IV osteoarthritis. The studies comprised a participant range of 27 to 150, with a cumulative enrolment of 657 individuals across the 15 studies. The main findings in group (1) indicated that the intra-articular HA injections administered to individuals with GH-OA, resulted in a significant improvement in both pain relief and shoulder function when compared to baseline. These improvement were observed in the short-term follow-up at six and 12 weeks, and four studies showed sustained benefits up to six months. The intervention of HA injection compared to PRP showed similar improvements in pain, disability, and functional impairments with no differences between interventions. The meta-analysis focused on categories (2) to (4) and highlighted the effectiveness of HA injection compared to comparative interventions or control groups. When comparing HA injections combined with PT to PT alone, the results indicated superior scores in patients with shoulder OA, showing an overall effect size (ES) of 4.43 (95% CI: 1.89 to 6.97, p=0.00006). Hyaluronic acid injections appeared to enhance the effects of PT on pain and shoulder function. Visual Analogue Scale (VAS) pain scores demonstrated a significant improvement in the ES of HA compared to corticosteroid injections (-1.47; 95% CI: -2.39 to -0.55, p=0.002). However, no significant ES of HA was observed in terms of the VAS improvement compared to control groups receiving no treatment or placebo injection (-2.30; 95% CI: -6.37 to 1.76, p=0.27).[44]

Another systematic review and meta-analysis conducted by Zhang B et al. (2019) aimed to comprehensively review the literature evaluating the efficacy of HA in terms of both

pain relief and safety for **patients with glenohumeral OA**. Electronic searches were performed across four databases, covering data up to January 16, 2018. Studies of patients aged over 18 with primary glenohumeral OA who received intra-articular HA injections were included. Fifteen studies, including 1,594 patients, met the criteria. The included studies consisted of five RCTs, six prospective cohort studies, one retrospective cohort study, and three case series. Meta-analysis was performed on seven eligible studies, which included two RCTs, four prospective cohort, and one retrospective cohort study, with a total of 1,001 participants. Three studies reported the severity of osteoarthritis, with two studies included individuals with grade I, II or III osteoarthritis, one study enrolled participants with grade II, III or IV, and five studies did not specified the stage of osteoarthritis. The administered dose (ranging from 2ml to 8ml) and type of HA varied among studies. Ten studies described **the injection technique used**: image guided technique (two studies), blind technique (seven studies), and a combination of both (one study). **The injection approach** was described in eight studies, with four used a posterior approach, two used an anterior approach, and two left the approach up to the clinician's discretion. The administration of HA injection demonstrated a significant decrease in the mean difference (MD) of VAS pain score at 3 months (MD: 26.2 mm; 95% CI: 22.0 to 30.3 mm) and at 6 months (MD: 29.5 mm; 95% CI: 25.5 to 33.4 mm) compared to baseline. A subgroup analysis by the type of control group (corticosteroid, phosphate-buffered saline, and no control) was performed, revealing significant improvement at 3 months for corticosteroid (MD: 27.0 mm; 95% CI: 21.2 to 32.8 mm; I^2 = 86%), phosphate-buffered saline (MD: 24.7 mm; 95% CI, 21.3 to 28.1 mm; I^2 = 10%), and the no control group (MD: 28.0 mm; 95% CI: 15.3 to 40.7 mm; I^2 = 0%). There were nine studies consisting of two RCTs and seven observational studies, reported functional outcomes with diverse population-based measures using different scales. All studies reported an improvement in functional outcome after HA administration. Among the seven studies with qualitative data, only four found statistically significant improvements in functional outcome between baseline and 6-months follow-up. Similar clinical improvements were observed in the intervention and control groups, suggesting that these improvements may not be directly related to HA.[45]

Kubo T et al. (2022) conducted a double-blind randomised controlled trial to evaluate the efficacy and safety of intra-articular diclofenac etalhyaluronate (DF-HA) in **patients with osteoarthritis affecting the hip, ankle, shoulder, or elbow**. Participant enrolment occurred between September 2017 and March 2019 at 44 study sites, though the total study duration was unspecified. Inclusion criteria involved individual's aged 20 years and older experiencing joint pain for at least six months in the hip, ankle, shoulder, or elbow, with numerical rating scale (NRS) for pain ranging from 5 to 9 in the target joint. In patients with OA involving multiple joints, only one joint was treated and assessed in this study. A total of 290 patients were randomised to receive either DF-HA (n=146) or placebo (n=144). The distribution of osteoarthritis across the study groups (DF-HA vs placebo) included 46 vs 44 for the hip, 30 vs 30 for the ankle, 45 vs 45 for the shoulder, and 25 vs 25 for the elbow. The DF-HA group received three

injections of 3ml sodium citrate buffer with 30mg DF-HA, while the placebo group received only 3ml sodium citrate buffer in the target joint cavity every four weeks (at weeks 0, 4, and 8). The study intervention was administered by **an orthopaedic surgeon** using the recommended approach of ultrasound- or fluoroscopy-guided injection, with blind injection was allowed for the ankle, shoulder, and elbow joints. However, it is worth noting that the differences in viscosity between the drug and placebo might have enabled the treating investigator to distinguish the intervention. To maintain blinding, outcome assessors were different from the investigator who administered the study drug. Assessments were conducted at 12 weeks after the first injection. The mean changes (DF-HA versus placebo) from baseline NRS for pain at 12 weeks after HA injection were -2.90 vs -2.10 for the hip; -1.96 vs -1.89 for the ankle; -1.96 vs -1.89 for the shoulder; and -2.28 vs -2.89 for the elbow joints, respectively. Between-group difference from baseline NRS after 12 weeks of HA injection were analysed and reported for hip joint OA (Difference in Least-square mean: -0.81, 95% CI: -1.48 to -0.13); ankle joint: -0.07 (95% CI: -1.03 to 0.89); shoulder joint: 0.15 (95% CI: -0.48 to 0.78); and elbow joint: 0.61 (95% CI: -0.41 to 1.62). A statistically significant difference for pain was observed only in the hip joint. Functional outcomes were based on joint-specific endpoints questionnaire and reported as mean changes over 12 weeks after the first injection of the study drug. For the hip joint, Western Ontario and McMaster Universities Osteoarthritis 3.1 index (WOMAC) assessment showed a greater improvement in the DF-HA group than in the placebo group. The functional assessments for other joints comprised of Self-Administered Foot Evaluation Questionnaire (SAFE-Q) for the ankle, Shoulder36 for the shoulder, and Patient-Rated Elbow Evaluation (Japanese Version) (PREE-J) for the elbow, which reported no clear improvement between the DF-HA group and the placebo group. The patient global assessment score, Short Form Health Survey 36-Item (SF-36) physical component score, EuroQol 5-dimensions (EQ-5D) quality of life score, and acetaminophen consumption for patients with hip joint OA were better in the DFHA group than placebo. In all other joint OA, the patient global assessment score improvement was unclear in both the DFHA and placebo groups.[46]

Tortato S et al. (2022) conducted a six-month single-blinded, randomised controlled trial to evaluate the effect of intra-articular hyaluronic acid injection on **primary shoulder osteoarthritis**. The study involved 86 patients, with 77 participants were randomised into either Hyaluronic acid group (HA group) or the Triamcinolone group (T group). Glenohumeral arthritis was classified according to the Samilson and Prieto Classification. In the HA group, 61% had mild and moderate OA (classified as “non-severe”), and 39% had severe OA. In the T group, 50% were classified as “non-severe”, and 50% as “severe” (Table 5). The HA group received a single IA injection of hylan G-F 20 (48 mg / 6 ml), while the T group received a single-dose IA injection of triamcinolone hexacetonide (20 mg / 1 ml, diluted in 5 ml saline). The procedures were **performed by the same attending physician using ultrasound guidance**. Follow-up assessments at 1 week, 1 month, 3 months, and 6 months included evaluations of pain, range of motion and shoulder function. Visual Analogue Scale (VAS) scores indicated pain

improvement in 76% of HA group patients after 1 month, and 71% after 6 month. In the T group, 76% showed pain improvement after 1 month, and decreasing to 32% after 6 months. Both groups exhibited reduced general VAS for pain, especially in cases of mild and moderate arthritis in the HA group (initial mean values: 8.1, reduced to 4.9 after 6 months). The VAS scores for pain during movement reported improvement in 76% of HA group patients after 1 month and 63% after 6 months. Night pain VAS score indicated improvement in 73% after 1 month and 66% after 6 months in the HA group. Reductions in pain scores for movement and night pain were observed at 1, 3, and 6 months, particularly in individuals with mild and moderate degree of osteoarthritis. Evaluation of questionnaire scores (Constant-Murley shoulder score, University of California-Los Angeles (UCLA) shoulder scale, and Shoulder Pain and Disability Index (SPADI) score) revealed gradual improvement up to 6 months after HA injection compared to the initial month's improvement in the non-severe group. There was no statistical difference in range of motion (anterior elevation, lateral rotation, and abduction) between the two study groups.[47]

Table 7: Outcomes of included studies for glenohumeral osteoarthritis

Author / Study design	No. of studies (No. of patients)	Study group	Outcomes
Familiari F et al. (2023) SR & MA	15 (657)	Diagnosis of: • Glenohumeral OA (9 studies) • Glenohumeral OA with KL grade II or III (2 studies) • Glenohumeral OA with KL grade I, II or III (1 study) • Glenohumeral OA with KL grade II, III or IV osteoarthritis (1 study) • Arthritic painful shoulder (1 study) • Cuff tear arthropathy (1 study)	**HA injections (single-arm open-label trials):** A significant improvement in both pain relief and shoulder function when compared to baseline. These improvement were observed in the short-term follow-up at six and 12 weeks, and four studies showed sustained benefits up to 6 months. **HA injections + PT vs PT alone:** Superior scores in HA + PT group with an overall effect size (ES) of 4.43 (95% CI: 1.89 to 6.97, p=0.00006). **HA injection vs Corticosteroid injection:** VAS pain scores demonstrated a significant improvement in the ES of HA compared to corticosteroid injections (-1.47; 95% CI: -2.39 to -0.55, p=0.002) within the first 6 months **HA injection vs control groups receiving no treatment or placebo injection:** No significant ES of HA was observed in VAS score compared to control groups (-2.30; 95% CI: -6.37 to 1.76, p=0.27). **HA injection vs PRP:** Showed similar improvements in pain, disability, and functional impairments with no differences between interventions.
Zhang B et al. (2019) SR & MA	15 (1,594)	Primary glenohumeral OA • Glenohumeral OA stage I, II, or III (2 studies) • Glenohumeral OA stage II, III, or IV (1 study) • 5 studies do not specified the OA stage	HA injection demonstrated significant decreased in VAS pain score compared to baseline: • **At three months** (MD: 26.2 mm; 95% CI: 22.0 to 30.3 mm) • **At six months** (MD: 29.5 mm; 95% CI: 25.5 to 33.4 mm) HA injection showed improvement in functional outcome, with four studies reported significant improvement at 6-months compared to baseline. However, similar clinical improvements were noted in both the intervention and control groups, suggesting that these improvements may not be directly attributable to HA.
Kubo T et al. (2022) RCT	(290)	Hip OA • Primary or secondary OA with early (mild articular wear) or advanced OA	**Primary outcome: Pain** **Mean change from baseline NRS after 12wk:** Hip: DFHA: -2.90 vs placebo: -2.10 Ankle: DFHA: -1.96 vs placebo: -1.89

Author / Study design	No. of studies (No. of patients)	Study group	Outcomes
		(advanced articular wear). Ankle OA • Primary or secondary talocrural OA due to trauma and radiographically as stage II (partial narrowing of the joint space) or stage III (partial disappearance of the joint space) varus ankle OA. Shoulder OA • Primary or secondary glenohumeral OA due to trauma or grade ≥4 rotator cuff tear according to Hamada classification Elbow OA • Primary or secondary OA due to trauma and radiographically as KL grade II or III.	Shoulder: DFHA: -1.84 vs placebo: -1.99 Elbow: DFHA: -2.28 vs placebo: -2.89 **Mean changes difference between groups from baseline NRS after 12 weeks of HA injection:** **(Difference in Least-square mean, 95% CI)** Hip: -0.81 (95% CI: -1.48 to -0.13) – statistically significant Ankle: -0.07 (95% CI: -1.03 to 0.89) Shoulder: 0.15 (95% CI: -0.48 to 0.78) Elbow: 0.61 (95% CI: -0.41 to 1.62) **Secondary outcome** The mean changes from baseline in joint-specific questionnaires over 12 weeks after the first injection of the study drug: **Hip (WOMAC)**: a greater improvement in the DF-HA group than in the placebo group was observed for all sub scores. **Ankle (SAFE-Q), Shoulder (Shoulder36), Elbow (PREE-J)** no clear improvement noted between DF-HA and placebo. Only in hip OA, the patient global assessment score, SF-36 physical component score, EQ-5D QOL score, and acetaminophen consumption were better in the DFHA group than in placebo. In all other joint OA, the patient global assessment score improvement was equivocal in both group DFHA and placebo.
Tortato S et al. (2022) RCT	(77 patients with 77 shoulders)	Primary glenohumeral OA HA group (degree of OA) • 9 (24%) mild • 14 (37%) moderate • 15 (39%) severe Triamcinolone group • 4 (12.5%) mild • 12 (37.5%) moderate • 16 (50%) severe Non-severe group = mild and moderate OA Severe group = severe OA	**Average overall pain by VAS score:** HA group: 76% of patients had pain improvement after 1 month, 71% had improvement after 6 month. Triamcinolone group: 76% of patients had pain improvement after 1 months and 32% had improvement after 6 month. **Average VAS score of pain during movement** 76% patient receiving HA injection had pain improvement after 1 month, 63% had improvement after 6 month. **Average VAS score night pain** 73% of patient receiving HA injection had pain improvement after 1 month, 66% had improvement after 6 month. **Evaluation of questionnaire scores** (CMS score, UCLA shoulder scale, and SPADI score) revealed gradual improvement up to 6 months after HA injection compared to the initial month's improvement in the non-severe group. No statistical difference regarding improvement in **range of motion (anterior elevation, lateral rotation, and abduction).**

OA: Osteoarthritis, KL: The Kellgren and Lawrence classification system, HA: hyaluronic acid, PT: physical therapy, PRP: platelet-rich plasma, NRS: Numerical Rating Scale, DFHA: diclofenac etalhyaluronate, VAS: Visual Analogue Scale, OA: osteoarthritis, CMS: Constant-Murley Shoulder Score, UCLA: University of California-Los Angeles shoulder scale, SPADI: Shoulder Pain and Disability Index

Table 7 presents findings from the four studies on glenohumeral OA. In summary, it is suggested that IA HA may effectively reduce pain and enhance shoulder function compared to baseline. Combining physical therapy with IA HA demonstrated superior pain relief improvement. However, the control group, which received IA corticosteroid or triamcinolone injections, or placebo, also demonstrated clinical improvements in pain relief and shoulder function. This suggests that a significant placebo effect may be present with respect to the IA shoulder injections. The results indicated better and longer-lasting outcomes, up to 6 months, for patients receiving hyaluronic acid, particularly those with **mild to moderate osteoarthritis**. There was no significant

difference in the shoulder range of motion improvement with IA HA injection. **The IA injection technique primarily** used image-guided methods, including ultrasound or fluoroscopy guidance, blind techniques, or a combination of both. **The described injection approaches** mainly utilised a posterior method, followed by an anterior approach, or left to the clinician's discretion. Skilled physicians or orthopaedic surgeons were responsible for administering the injections.

7.1.2 Hip osteoarthritis

(a) Pain

In the study by Belk JW et al. (2022), there was no statistically significant difference between IAHA and PRP regarding pain improvement, as measured by WOMAC pain and VAS pain scores. The standardised mean differences (SMD) of 0.43 (p=0.35) for WOMAC pain and 5.9 (p=0.39) for VAS pain indicated comparable efficacy between the two interventions. Conversely, Sambe HG et al. (2023) revealed a nuanced picture. While patients receiving HA experienced higher overall WOMAC-pain scores, PRP exhibited superiority at the 6-month mark in WOMAC pain (SMD -0.38, p=0.03) and VAS pain (SMD -0.50, p<0.01). Intriguingly, at 12 months, no significant differences were noted (SMD -0.85, p=0.09).[48]

Adding another layer to the discussion, Ali SE et al. (2021) demonstrated that the overall effect size for VAS scores was statistically non-significant (SMD -0.056; 95% CI; -0.351, 0.239; p=0.709). The I^2 value for heterogeneity was negligible and non-significant (I^2= 0%, p=0.788), providing a degree of consistency across the studies.[50] The findings from Leite VF et al. (2018) reveals very low evidence suggesting that HA is not superior to placebo for pain at 3 months, with a standardised mean difference (SMD) of -0.06 (95% CI, -0.38 to 0.25, p = 0.69). In the comparison with PRP, the study reports low evidence that HA is not superior for pain at 1 month. Additionally, there is very low evidence suggesting that HA is not superior to PRP for pain at 6 and 12 months. The mean difference in VAS scores is -0.05 (95% CI, -0.81 to 0.71) at 1 month, 1.0 (95% CI, -1.5 to 3.50) at 6 months, and 0.81 (95% CI, -1.11 to 2.73) at 12 months. Furthermore, the study establishes high evidence supporting the notion that HA is no different from methylprednisolone for pain at 1 month, with an SMD of 0.02 (95% CI, -0.18 to 0.22, P = 0.85).[53]

Medina-Porqueres I et al. (2021) introduced further complexity, with significant improvement favouring PRP over HA at 6 months.[51] In the study by Wu et al. (2021), which delved into the molecular weight of hyaluronic acid and its impact on viscosupplementation efficacy in hip osteoarthritis, all three HA groups exhibited significant improvements in VAS scores at 1, 3, and 6 months.[52] However, the

considerable heterogeneity observed across studies underscores the need for cautious interpretation.

In synthesising these diverse findings, it becomes evident that while IAHA demonstrates effectiveness in pain reduction for hip OA, the variability in outcomes, durations, and heterogeneity among studies calls for a nuanced understanding of IAHA's role in managing hip OA pain. The intricate interplay of factors necessitates further research with standardised methodologies, longer-term evaluations, and larger sample sizes to provide more definitive conclusions on IAHA's efficacy in this context. This multifaceted exploration underscores the need for precision and individualised approaches in the utilisation of IAHA for hip OA pain management.

(b) Functional

Ali SE et al. (2021) scrutinised the functional disability using the Lequesne Index. The overall SMD was statistically non-significant (SMD -0.114; 95% CI; -0.524 to 0.296; p=0.585), suggesting that IAHA did not significantly alter functional outcomes based on this index. The I^2 value for heterogeneity was negligible and non-significant (I^2 =0%, p=0.945) from two of the four trials.[50]

Sambe HG et al. (2023) examined the Harris Hip Score (HHS) to gauge functionality. At 1-2 months, HHS function was not reported. Platelet-rich plasma yielded significantly greater improvements in VAS pain compared to IAHA (SMD -0.50, p<0.01). However, at 6 and 12 months, there were no significant differences in HHS between IAHA and PRP groups (SMD 0.02, p=0.93; SMD -0.31, p=0.73).[49]

Belk JW et al. (2022) delved into functionality using WOMAC and Harris Hip Score. No significant differences were found between IAHA and PRP for improvement in WOMAC function (SMD 0.35, p=0.13) or Harris Hip Score (MD -0.81, p=0.39).Examining hip survivorship, Belk et al. found that at 2 years, hip survivorship was higher with PRP than IAHA. The survivorship rate with PRP was 0.84 (95% CI 0.69-1.00) compared to 0.41 (95% CI 0.20-0.83) with IAHA, based on one study.[48]

Medina-Porqueres I et al. (2021) focused on WOMAC scores to evaluate function. At 2 and 6 months, one study reported that the PRP group improved significantly more than the HA group on WOMAC total and sub scores.[51]

Wu YZ et al. (2021) assessed functionality using the Lequesne Index. Both the moderate-molecular-weight (MMW) and high-molecular-weight (HMW) groups showed significant improvements at the 3-month follow-up, with HMW outperforming low-molecular-weight (LMW) and MMW groups (MD = 5.64, 95% CI = 5.15-6.13, P < 0.00001 for HMW group). Furthermore, at various time points, improvements in Lequesne Index were significant in all groups except the LMW group, with HMW

consistently demonstrating superior efficacy compared to other molecular weights (P = 0.001). The efficacy of HMW group was significantly better than the LMW (P = 0.003) or MMW group (P = 0.03). However, there was no significant difference between the LMW and MMW groups (P = 0.42).[52]

Leite VF et al. (2018) reveals that there is low level of evidence indicating no difference between HA and methylprednisolone for the Outcome Measures in Rheumatoid Arthritis Clinical Trials - Osteoarthritis Research Society International Responders Index at 1 month, with an RR of 0.44 (95% CI, 0.10-1.95, P = 0.28).[53]

In summary, the effectiveness of IAHA for hip osteoarthritis presents a complex landscape with varying outcomes across studies. Investigations into functional outcomes by Ali SE et al. (2021), Sambe HG et al. (2023), Belk JW et al. (2022), Medina-Porqueres I et al. (2021), and Wu YZ et al. (2021) yield diverse results. Ali SE et al. (2021) and Belk JW et al. (2022) reported no significant differences in functional indices between IAHA and comparators, while Sambe HG et al. (2023) find platelet-rich plasma (PRP) to be superior to IAHA in early pain reduction. Notably, Belk JW et al. (2022) introduced the dimension of hip survivorship, suggesting PRP's superiority at the 2-year mark. Wu YZ et al. (2021) delved into molecular weight, indicating higher efficacy for HMW-HA. Leite VF et al. (2018) contributed evidence, suggesting IAHA's limited superiority over placebo and PRP. This nuanced conclusion underscores the heterogeneity of findings, emphasising the need for cautious interpretation and prompting further research to elucidate the specific conditions under which IAHA may offer optimal benefits for individuals with hip OA. Table 8 provides an overview of the results.

Table 8: Outcomes of included studies for hip osteoarthritis

Author / Study design	No. of studies (no. of patients)	Pain		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
Belk JW et al. (2022) / Systematic Review and Meta-analysis	6 studies (5 level I, 1 level II)	There were no significant differences between groups in the weighted improvement of any outcome score (WOMAC, VAS, or HHS) between pre-injection and post injection. Even after excluding one study with the highest risk of bias to eliminate heterogeneity, the pooled sub analysis demonstrated no significant differences in the WOMAC sub scores between the PRP and HA groups. A pooled sub analysis that isolated patients treated with leukocyte-poor PRP found no significant differences between the groups treated with PRP and HA.			
Sambe HG et al. (2023) / Systematic Review and Meta-analysis	7 RCTs	No significant differences in WOMAC pain scores were noted at one to two months (SMD = 0.09, CI = -0.24 to 0.43; p = 0.59) No significant differences in VAS between the PRP groups and the HA groups were observed at one to two months (SMD = -0.22, CI = -0.49 to 0.04; p = 0.10).	The PRP group experienced a significantly lower standard mean WOMAC pain score (SMD = -0.38, CI = -0.64 to -0.13; p = 0.03). No significant differences in WOMAC pain scores were noted at 12 months (SMD = -0.85, CI = -1.81 to 0.12; p = 0.09).	-	No statistically significant standard mean difference in HHS between the PRP and HA groups at six months (SMD = 0.02, CI = -0.40 to 0.44; p = 0.93), and at 12 months (SMD = -0.31, CI = -0.32 to 0.22; p = 0.73).

Author / Study design	No. of studies (no. of patients)	Pain		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
			Patients on PRP showed a slight improvement in their VAS scores at six months (SMD = -0.50, CI = -0.89 to -0.12; p < 0.01). No significant differences in VAS between the PRP groups and the HA groups were observed at 12 months (SMD = -0.22, CI: -0.63 to 0.19; p = 0.29).		
Medina-Porqueres I et al. (2021) / Systematic Review and Meta-analysis	4 trials (334 participants, 340 hips)	**PRP on pain and function** Early evaluations and follow up (1, 2, and 3 months after last injection) showed a consistency significant improvement of VAS, HHS, and WOMAC, except for WOMAC score in one study (p<0.01). Two studies reported PRP is better against comparative treatment than in control groups. One study reported equally significant changes in both PRP and HA groups with no significant differences between them. Longer term follow up (4*, 6, and 12 months), diverse results were obtained.			
Ali SE et al. (2021) / Systematic Review and Meta-analysis			Median follow up: 6.25 (3–12) months. Three of the four trials measured subjective pain using the VAS score on a scale of either 0–10. The overall SMD for VAS score was statistically non-significant (SMD -0.056; 95% CI; -0.351 to 0.239; p=0.709). The I^2 value for heterogeneity was negligible and non-significant (I^2=0%, p=0.788)		Median follow up: 6.25 (3–12) months. Two of the four trials measured functional disability using the Lequesne index. The overall SMD for Lequesne index was statistically non-significant (SMD -0.114; 95% CI; -0.524 to 0.296; p=0.585). The I2 value for heterogeneity was negligible and non-significant (I^2 =0%, p=0.945)
Wu YZ et al. (2021) / / Systematic Review and Meta-analysis		All the 3 HA groups had a significant improvement in VAS at the 3-month follow-up when compared with the baseline level (trial = 4, I^2 = 1%, MD = 1.12, 95% CI = 0.73 to 1.52, p<0.00001 for LMW group; trial = 3, I^2 = 0%, MD = 2.17, 95% CI = 2.07 to 2.28, P < 0.00001 for MMW group; trial =4, I^2 = 74%, MD = 3.08, 95% CI = 1.98 to 4.19, P < 0.00001 for HMW group). There was a significant difference among these 3 groups (p < 0.00001).	All the 4 HA groups had a significant improvement in VAS at the 6-month follow-up when compared with the baseline level (trial = 3, I^2 = 20%, MD = 1.68, 95% CI = 1.15 to 2.22, P < 0.00001 for LMW group; trial = 4, I2 = 0%, MD = 1.93, 95% CI = 1.82 to 2.04, P < 0.00001 for MMW group; trial = 3, I^2 = 0%, MD = 2.98, 95% CI = 2.24 to 3.73, P < 0.00001 for HMW group; trial = 2, I 2 = 23%, MD =	The MMW and HMW groups had a significant improvement in Lequesne index at the 3-month follow-up when compared with the baseline level (trial = 3, I^2 = 73%, MD = 1.85, 95% CI = −0.62 to 4.33, P = 0.14 for LMW group; trial = 3, I^2 = 55%, MD = 3.19, 95% CI = 1.09 to 5.29, P = 0.003 for MMW group; trial = 3, I 2 = 0%, MD =	There were 4 HA groups at the 6-month follow-up, including LMW, MMW, HMW, and UHMW groups. They had a significant improvement in Lequesne index when compared with the baseline level except for the LMW group (trial = 3, I 2 = 46%, MD = 1.69, 95% CI = −0.06 to 3.45, P = 0.06 for LMW group; trial = 3, I 2 = 48%, MD = 3.30, 95% CI = 1.49-5.10, P = 0.0004 for MMW group; trial = 3, I

Author / Study design	No. of studies (no. of patients)	Pain		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
			1.81, 95% CI = 1.15-2.46, P < 0.00001 for UHMW group). There was a significant difference among these 4 groups (P = 0.03).	5.64, 95%CI = 5.15-6.13, P < 0.00001 for HMW group).	2 = 0%, MD = 5.73, 95% CI = 4.28-7.18, P < 0.00001 for HMW group; trial = 2, I 2 = 0%, MD = 2.16, 95% CI = 1.24-3.07, P < 0.00001 for UHMW group).
Leite VF et al (2018) / Systematic review and meta-analysis		**HA vs Placebo** Not significant at 1, 2 and 3 month follow up as measured by VAS **HA vs PRP** Pooled data of VAS at 1, 6, and 12 months did not reveal a difference between groups **Ha vs methylprednisolone** 1 study indicated the superiority of methylprednisolone over HA at 1 month, however, data assessed using SMD did not show any significant differences.	**HA vs Placebo** Not significant at 6 month follow up as measured by VAS **HA vs PRP** Pooled data of VAS at 1, 6, and 12 months did not reveal a difference between groups	**HA versus mepivacaine** Lequesne index at 3 months, -1.38-2.46 (P<.001);	**HA versus mepivacaine** Lequesne index at 6 months, -2.47-7.9 (P<.05).

7.1.3 Knee osteoarthritis

Xue Y et al. (2023) conducted a network meta-analysis comparing the effectiveness of various intra-articular injections for **mild to moderate knee osteoarthritis**. They systematically searched seven databases until December 2021, included 16 RCT articles involving 1,652 patients. The overall risk of bias was low, and the quality of the articles was assessed as good. The interventions comprised IA injections of PRP, platelet-rich plasma-derived growth factor (PRGF), HA, ozone, and corticosteroids, which were also included in the comparison group. The primary outcomes were changes in the VAS pain score and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) from baseline. In the **VAS score group**, SUCRA probabilities indicated that the combination of IA HA + PRP (SUCRA score: 96.8%) was most superior in reducing VAS pain score, followed by PRGF (72.5%), PRP (70.6%), HA (31.7%), CS (21.8%), and ozone (6.5%). However, no significant difference were found between combination IA injection HA and PRP versus PRP alone, and PRP versus PRGF. Platelet-rich plasma significantly reduced VAS score when compared with HA (WMD 1.3, 95% CI: 0.55 to 2.55) and corticosteroids (WMD 4.85, 95% CI: 4.02 to 5.08). For **WOMAC total score**, IA PRGF injection (SUCRA score: 84.9%) had the highest probability of reducing the WOMAC total score, followed by PRP (72.9%), HA (60.3%), ozone (38.1%), HA + PRP (29.7%), and CS (14.1%). Platelet-rich plasma significantly reduced WOMAC scores when compared with combination HA and PRP (WMD 2.18, 95% CI: 0.55 to 3.81), corticosteroid (WMD 14.76, 95% CI: 12.11 to 17.41), and ozone (WMD 9.16, 95% CI: 6.89 to 11.43). In the analysis of WOMAC sub-domains, IA PRP

injection had the highest likelihood of being the best intervention in reducing WOMAC pain (SUCRA score: 84.7%), stiffness (SUCRA score: 95.1%), and function (SUCRA score: 98.5%0) scores compared with IA injections of HA, corticosteroid, ozone, combination HA and PRP, and PRGF.[54] In this study, the effectiveness of IA HA injections was consistently ranked after platelet-rich plasma (PRGF or PRP) for pain relief and functional improvement in patients with knee osteoarthritis. The findings demonstrated that combining HA with PRP significantly reduces pain, though this combination has not been extensively researched.

Another network meta-analysis conducted by Lin X et al. (2022), the primary objective was to compare the effectiveness of various knee intra-articular injections in **patients aged 50 and above with knee osteoarthritis**. The study aimed to directly or indirectly assess the effectiveness of PRP, ozone, hyaluronic acid, and combined injections within the knee cavity. Subsequently, to provide insights into the ranking of these treatment measures for the clinical management of knee OA. They systematically reviewed five databases up to July 20, 2021, and identified a total of 33 RCTs involving 7,003 patients, with sample sizes ranging from 12 to 126 cases. The primary studies predominantly consist of single clinical effectiveness analyses and lack direct comparisons of comprehensive therapies involving PRP, ozone, and sodium hyaluronate, as well as their combinations. Hence, this network meta-analysis evaluated the differences in effectiveness between each individual therapy and combined treatment regimes. The review focused on assessing outcomes related to symptoms, pain, function, activity of daily living (ADL) and quality of life (QOL). The direct comparison contributing to the network meta-analysis were as follows: HA vs PRP + HA (25.0%), HA + ozone vs ozone (24.7%), PRP vs PRP + HA (23.0%), HA vs HA + ozone (12.5%), HA vs ozone (12.5%), HA vs PRP (2.3%). Platelet-rich plasma was more effective than hyaluronic acid and ozone in monotherapy, with a statistically significant difference (PRP vs ozone: OR = 2.89, 95% CI: 1.21 to 6.88). However, the effectiveness of ozone compared to HA was not statistically significant. Comparisons were also made between two combination therapies (PRP + HA, and HA + ozone) and three monotherapies (PRP, ozone, and HA). Both combination therapies were found to be superior and statistically significant compared to HA and ozone monotherapy treatments. The Surface Under the Cumulative Ranking (SUCRA) scores indicated the efficacy ranking as follows: PRP + HA (82.8%), HA + ozone (80.9%), PRP (60.9%), ozone (19.4%), and HA (6.1%). Thus, the findings suggested that combination therapies involving PRP + HA and HA + ozone were more effective than monotherapy. Additionally, PRP demonstrated greater effectiveness compared to ozone and HA in the context of knee OA monotherapy, while there was no significant difference in the effectiveness between ozone injection and HA monotherapy.[55] The results should be interpreted with caution due to the small sample sizes of the primary studies. Furthermore, most studies predominantly compared the combination of HA with ozone to HA alone, and PRP to HA. The authors also noted that the findings of this study need to be validated by a substantial number of well-designed and appropriate RCTs.

Belk JW et al. (2023) conducted a systematic review to compare the efficacy and safety of PRP, bone marrow aspirate concentrate (BMAC), and HA injections for **knee osteoarthritis treatment**. A systematic search was conducted across three databases up to August 15, 2022, identified a total of 27 RCTs with 2,396 patients that met the inclusion criteria. Among these trials, 1,042 patients received IA PRP injections with a mean age of 57.7 years and mean follow-up duration of 13.5 months. Additionally, 226 patients were treated with BMAC, with a mean age of 57.0 years and a mean follow-up of 17.5 months. The remaining 1,128 patients underwent IA HA, with a mean age of 59.0 years and a mean follow-up of 14.4 months. Analysis of patient-reported outcomes related to symptoms, pain, and functionality was conducted. **The non-network MA** revealed significant improvement in post-injection WOMAC score (MD -12.89, 95% CI: -16.78 to -9.01, p<0.00001, I^2=90%), VAS score (MD -9.51, 95% CI: -16.02 to -3.01, p<0.00001, I^2=98%), and subjective IKDC scores (MD 8.47, 95% CI: 6.14 to 10.80, p=0.0001, I^2=54%) in PRP recipients compared to HA group. Similarly, **network MA** demonstrated significantly better post-injection WOMAC score (SMD 0.9803, 95% CI: 0.6833 to 1.2774, p<0.001), VAS score (SMD 0.3696, 95% CI: 0.0310 to 0.7081, p=0.032), and subjective IKDC scores (SMD 0.98, 95% CI: 0.68 to 1.28, p=0.001) in patients who received BMAC compared to HA recipients. No significant differences in post-injection outcome scores were found when comparing PRP with BMAC. Sub-analysis within this review revealed that 60% of patients received LR-PRP experienced significant improvement in outcome scores post-injection compared to those who received HA. While, 46.7% of outcome scores in studies using LP-PRP resulted in significant improvement in PRP recipients compared to HA recipients.[56]

This review suggested that PRP is more effective than HA in treating OA. However, the comparative effectiveness between LP- and LR-PRP remains unclear. A limitation was that 21 out of 27 studies did not evaluate post-injection outcomes based on OA grades, thus preventing a sub-analysis according on these grades. Nonetheless, based on four studies, there was no significant difference in outcomes among patients with Kellgren-Lawrence grade 1, 2, or 3 OA at follow-up. It is important to note several factors that contributed to the moderate-to-high heterogeneity observed in these studies. These included differences in the administration techniques and strategies used for PRP, HA, and BMAC across the studies. Additionally, none of the included studies provided data on knee survivorship, specifically the number of patients who eventually required total knee arthroplasty after failed injection therapy.[56]

In their 2022 systematic review, Mojica ES et al. assessed the maximum medical improvement (MMI) and minimal clinically important difference (MCID) of various injectables in **symptomatic knee osteoarthritis** treatment. The searches were conducted across three databases in September 2020, yielded 79 studies with a total of 8,761 patients. All included studies were RCTs utilising VAS and WOMAC scores, both on 100-point scales, as clinical outcomes where lower scores indicated pain relief and

functional improvement. Clinical outcomes were compared at intervals from baseline to 4-6 weeks, 4-6 weeks to 3 months, 3 months to 6 months, and 6 months to 1 year. MCID represents the lowest outcome difference perceived as clinically important by the patient. The MCID thresholds used were 10.37 for the VAS score and 10.00 for the WOMAC score. While MMI is defined as the time point where patient progress reaches a plateau or the last time point in which patients experience improvement that reaches MCID. The injection protocols varied among the studies and included placebo, corticosteroid, low, middle, and high molecular weight hyaluronic acid (HA), leucocyte-poor platelet-rich plasma (LP-PRP), and leucocyte-rich platelet-rich plasma (LR-PRP).

The analysis revealed significant differences in the effectiveness of various injectable treatments for pain relief. Patients who received corticosteroid injections, middle-molecular weight hyaluronic acid (MMW-HA), and LR-PRP injections experienced peak pain relief at 4 to 6 weeks post-injection. In contrast, those who received LMW-HA, HMW-HA, and LP-PRP injections reached maximum pain relief at 3 months, with LP-PRP had the lowest score among all treatments. Significant differences in the MMI and MCID for VAS scores were observed for all treatments except saline injection from baseline to 4-6 weeks. Low-molecular weight-HA showed superior pain relief compared to LP-PRP and corticosteroid from 4-6 weeks to 3 months. However, from 6 months to 1 year, LP-PRP outperformed both HA and corticosteroid. When examined the **WOMAC scores**, the lowest score were observed with CS, LMW-HA, and MMW-HA at 4 to 6 weeks, and with HMW-HA and LP-PRP after 3 months. At 1 year, LR-PRP had the lowest WOMAC scores compared to other injection types. Although LP-PRP reached the lowest WOMAC score at 3 months, LR-PRP provided the best functional outcome at final follow-up of 1 year. This indicated that while LP-PRP offered short-term benefits, LR-PRP was more effective for long-term functional improvement. In contrast, HA treatments had varied results, with the maximum improvement occurred within 4 to 6 weeks. In summary, PRP injections were able to sustain pain relief and functional improvement for the long-term. While HA and corticosteroids provided good short-term relief but lack the longevity offered by PRP injections.

A meta-analysis conducted by Tan J et al. (2020) aimed to compare the effectiveness and safety of platelet-rich plasma (PRP) and hyaluronic acid (HA) in **adults with knee osteoarthritis**. The secondary objective was to identify the most effective and safe protocol through subgroup analyses of different doses, types and times of PRP interventions and various grades of OA. The meta-analysis included 26 RCTs with a total of 2,430 patients, ranging from 21 to 192 patients each across the studies. Only studies with intervention group of PRP and control group of HA were included, with 21 studies involved grade 1-3 OA, four studies included patients with up to grade 4, and a study used Karnofsky performance status. The administration of PRP and HA varied among studies. The WOMAC total scores were analysed at different time points of 1, 3, 6, and 12 months. Results indicated that PRP showed significant improvement in **WOMAC total scores** at 3 months (MD -5.04, 95% CI: -8.82 to -1.26; p=0.009), 6

months (MD -8.52, 95% CI: -11.17 to -5.87; p<0.00001), and 12 months (MD -10.52, 95% CI: -13.77 to -7.27; p<0.00001) compared to HA. For **WOMAC pain scores,** PRP group also demonstrated superior improvement at 6 months (MD -1.17, 95% CI: -1.99 to -0.35 p=0.005) and 12 months (MD -1.62, 95% CI: -2.26 to -0.98; p<0.00001). Additionally, PRP yielded more improvement in **WOMAC stiffness score** at 6 months (MD -0.39, 95% CI: -0.74 to -0.04; p=0.03) and 12 months (MD -0.84, 95% CI: -1.16 to -0.53; p<0.00001), and **WOMAC physical function score** at 3 months (MD -1.90, 95% CI: -2.54 to -1.26; p<0.00001), 6 months (MD -3.15, 95% CI: -4.95 to -1.35; p=0.0006) and 12 months (MD -7.32, 95% CI: -9.98 to -4.66; p<0.00001). PRP also provided better knee pain relief than HA, as shown by **VAS scores** at 3, 6 and 12 months, and **EQ-VAS scores** at 6 and 12 months of treatment. Various other measures were employed to demonstrate function and disability improvement, including International Knee Documentation Committee (IKDC) Score, Tegner Score, Lequesne Scale, and Knee Injury and Osteoarthritis Outcome Score (KOOS). The **Tegner score and IKDC scores** favoured PRP, while the **Lequesne Scale and KOOS score** showed no significant difference between the two groups. Lastly, **Satisfaction Rate** was reported in four studies, revealing no significant difference between the PRP and HA groups. Subgroup analyses were conducted on varying doses, types, and timing of PRP interventions, as well as different grades of OA, however, no significant findings.[58] This study demonstrated that for non-surgical treatment of knee OA, IA PRP significantly reduced pain and improved function compared to HA. There was no significant difference in adverse events between the two groups, with comparable safety. The PRP's WOMAC total scores surpassed the minimal clinically important difference (MCID, difference of 6 points) compared to HA group in the long-term, with improvement observed at 6 months (MD: -8.52) and 12 months (MD: -10.52). However, limitations of this review should be noted, including the small sample sizes, short follow-up time of the included studies, and significant heterogeneity in the WOMAC total, WOMAC pain, WOMAC stiffness, WOMAC physical function, VAS, EQ-VAS, and IKDC scores.

Table 9: Outcomes of included studies for knee osteoarthritis

Author / Study design	No. of studies (No. of patients)	Study group	Outcomes
Xue Y et al. (2023) Network Meta-analysis	16 RCTs (1,652)	Diagnosis of: • Mild to moderate knee OA (the Kellgren-Lawrence Radiology Scale system score ranged from 1-3) • PRP, n=374 • HA, n=616 • Ozone group, n=150 • CS group, n=159 • PRGF group, n=219 • HA+PRP group, n=134	**VAS pain score** Highest SUCRA probabilities for reducing VAS score: • HA + PRP (SUCRA score: 96.8%) PRP significantly reduced VAS score when compared with HA and CS **WOMAC total score** Highest SUCRA probabilities for lowering WOMAC total score: • PRGF (84.9%) PRP significantly reduced WOMAC total score when compared with HA+PRP, CS, and ozone. **WOMAC function, pain, and stiffness score** PRP significantly reduced WOMAC function, pain and stiffness scores.

Author / Study design	No. of studies (No. of patients)	Study group	Outcomes
Lin X et al. (2022) Network Meta-analysis	33 RCTs (7,003)	Knee OA • The inclusion criteria did not specify the OA grading.	**Combination therapies** involving PRP + HA and HA + ozone were more effective than monotherapy. **Monotherapy:** PRP was more effective than ozone and HA. SUCRA scores: PRP + HA (82.8%), HA + ozone (80.9%), PRP (60.9%), ozone (19.4%), and HA (6.1%). The authors suggested that, in clinical practice, this approach may be preferable for patients with Kellgren-Lawrence grade 2-3.
Belk JW et al. (2023) SR and MA	27 RCTs (2,396)	Knee OA • 21 of 27 studies did not analyse post-injection outcomes based on OA grades. ○ 4 studies: Kellgren-Lawrence grade 1-3 ○ 2 studies: KL grade 1-4 • PRP, n=1.042 • BMAC, n=226 • HA, n=1,128	Non-network MA: Significant improved post-injection **WOMAC, VAS,** and **Subjective IKDC scores** in PRP group compared to HA group. Network MA: Significantly improvement post-injection **WOMAC, VAS,** and **Subjective IKDC scores** in patients who received BMAC compared to HA recipients. No significant differences in post-injection outcome scores when comparing PRP with BMAC. Outcomes by OA Grade Based on four studies, there was no significant difference in outcomes at follow-up among patients with grade 1, 2, or 3 OA.
Mojica ES et al. (2022) SR	79 RCTs (8,761)	Knee OA	**VAS pain score** The lowest score for various injections at time point: 4-6 weeks: CS, MMW-HA, LR-PRP 3 months: LMW-HA, HMW-HA, **LP-PRP** 3 months and 1 year: **LP-PRP** **WOMAC score:** The lowest score for various injections at time point of 4-6 weeks: CS, LMW-HA, MMW-HA 3 months: HMW-HA, **LP-PRP** 1 year: **LR-PRP**
Tan J et al. (2020) MA	26 RCTs (2,430)	Knee OA • 21 studies: Grade 1-3 • 4 studies: Grade1-4 • 1 study: used Karnofsky performance status of ≥80%	**WOMAC total, WOMAC physical function, and VAS scores:** • Favoured PRP at 3, 6, and 12 months **WOMAC pain, WOMAC stiffness, and EQ-VAS scores:** • Favoured PRP at 6 and 12 months **IKDC score, Tegner score:** Favoured PRP **Lequesne scale, KOOS score, Satisfaction Rate:** No significant difference between the PRP and HA groups.

OA: Osteoarthritis, HA: hyaluronic acid, PRP: platelet-rich plasma, PRGF: platelet-rich plasma-derived growth factor, CS: corticosteroid, SUCRA: Surface Under the Cumulative Ranking, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, VAS: Visual Analogue Scale, IKDC: International Knee Documentation Committee, KOOS: Knee Injury and Osteoarthritis Outcome Score

Summarising the findings from the five studies above on knee osteoarthritis (Table 9), they collectively highlight the effectiveness PRP injections as a superior non-surgical treatment option for knee osteoarthritis compared to hyaluronic acid. Across these studies, PRP consistently outperforms HA and other IA injections in reducing pain and improving function for patients with knee OA. Combination therapies involving PRP (e.g., PRP + HA) often demonstrate enhanced benefits compared to monotherapies. The studies highlight the superior efficacy of PRP, both as a monotherapy and in combination with HA, suggesting that PRP may be considered as a treatment option for knee OA. However, further research is needed to validate these findings, particularly regarding long-term outcomes and optimal combination protocols. The studies also indicated that HA provides good short-term relief but lacks the longevity offered by PRP injections.

7.1.4 Ankle osteoarthritis

Paget LD et al. (2023) conducted a systematic review aiming to evaluate the effectiveness of IAHA injections for ankle osteoarthritis. However, the study refrained from performing a meta-analysis to avoid potential biases. The review concluded that there is insufficient evidence to support the use of IAHA as a treatment for ankle OA. Among the five studies evaluated, only one had a low risk of bias, and only one study demonstrated a statistical benefit. However, none of these studies found clinically relevant effect-size differences for the Ankle Osteoarthritis Scale and WOMAC scores at 12 weeks, as none of the between-group differences exceeded the relevant minimum clinically important differences (MCIDs). Furthermore, no new randomised controlled trials (RCTs) have been published on the efficacy of intra-articular HA injections since the publication of previous reviews on injection therapy for ankle OA.[59]

Witteveen AG et al. (2015) conducted a review comparing IAHA injections with placebo (saline) across three studies, reporting a mean difference (MD) of 12.53 points favouring IAHA over placebo at six months, with a 95% CI of -23.84 to -1.22. While this demonstrates a statistically significant reduction in pain scores favouring IAHA, the clinical significance of this difference remains uncertain and requires further investigation. Additionally, at three months, a lower MD of 2.26 points was observed (95% CI -11.23 to 6.72), although this difference was not statistically significant. Furthermore, studies comparing IAHA injections with exercise therapy or botulinum toxin A (BoNT-A) injections showed mixed results, with no clear consensus on the effectiveness of IAHA for pain management in ankle OA. Similarly, the investigation into the efficacy of different doses of IAHA injections yielded inconclusive findings, with no statistically significant decrease in pain scores observed across the various dose groups. Overall, the limited data available preclude a robust synthesis of the evidence regarding the effectiveness of IAHA for pain reduction in ankle OA. Further research utilising rigorous study designs and larger sample sizes is needed to establish the efficacy of IAHA injections in effectively alleviating pain associated with ankle OA.[60]

In terms of function, when comparing IAHA injections to placebo (saline) across three studies (Cohen 2008; DeGroot 2012; Salk 2006), significant improvements were observed. At six months, the Ankle Osteoarthritis Scale (AOS) total score was notably lower by 12.53 points (MD) in favour of IAHA compared to placebo, with a 95% CI ranging from -23.84 to -1.22. Similarly, at three months, IAHA yielded a 2.26 points lower AOS total score (MD) compared to placebo, though the confidence interval ranged from -11.23 to 6.72, indicating some uncertainty in the effect size. Moreover, in comparison to exercise therapy, IAHA injections demonstrated significant benefits in improving physical function. At 12 months, the American Orthopedic Foot and Ankle Society

(AOFAS) score was notably higher by 13.10 points (MD) in favour of IAHA over exercise therapy, with a 95% CI ranging from 2.97 to 23.23.

Chang KV et al. (2013) conducted a comprehensive meta-analysis to assess the effectiveness of intra-articular hyaluronic acid (IAHA) injections for ankle OA. Their analysis, encompassing various study designs, revealed a pooled effect size of 2.01 (95% CI: 1.27 to 2.75) for improvement scores, primarily focusing on the Ankle Osteoarthritis Scale (AOS) and VAS score from baseline. This calculation was performed using a random-effects model due to significant heterogeneity observed across trials (I^2 = 92.1%, $p<0.0001$). Subgroup analysis indicated comparable effectiveness between RCTs and single-arm prospective studies, with pooled effect sizes of 2.33 (95% CI: 0.53 to 4.14) and 1.31 (95% CI: 0.59 to 2.03), respectively. However, when comparing IAHA with other treatments based on AOS and VAS, the pooled effect size was notably lower at 0.85 (95% CI: -0.13 to 1.83), derived from five studies with comparative designs. Subgroup analysis within three double-blind RCTs using saline as a reference therapy showed a slightly higher pooled effect size of 1.00 (95% CI: -0.87 to 2.87). These findings suggest a discrepancy in the efficacy of IAHA injections for ankle OA compared to other treatments, indicating the need for further research to elucidate the true effectiveness and comparative benefits of IAHA in managing ankle OA symptoms.[61]

Table 10 presents a summary of the findings from the included ankle OA studies.

Table 10: Outcomes of included studies for ankle osteoarthritis

Author / Study design	No. of studies (no. of patients)	Pain		Functional improvement	
		Short-term (< 6 months)	Long-term (≥ 6 months)	Short-term (< 6 months)	Long-term (≥ 6 months)
Paget et al. (2023) / Systematic Review	7 RCTs	Results were assessed using AOFAS (American Orthopaedic Foot and Ankle Society) score, AOS (Ankle Osteoarthritis Scale), and VAS (Visual Analog Scale). The evaluation was conducted at 12, 26, and 52 weeks across five studies. None of the studies found significant differences in the effectiveness of HA (hyaluronic acid) in treating ankle osteoarthritis.			
Witteveen et al. (2015) / Systematic review	6 blinded RCTs (3 double blinded RCTs which compared the IAHA to placebo (Cohen 2008; DeGroot 2012; Salk 2006).	**HA vs Placebo (Saline)** At three months (two studies: Cohen 2008 and DeGroot 2012; 92 participants) compared to control the total AOS score was 2.26 lower points lower (MD) (95% CI −11.23 to 6.72).	**HA vs Placebo (Saline)** (Cohen 2008 and Salk 2006; 45 participants) compared to control at six months (primary outcome), the AOS total score was 12.53 points lower mean difference (MD) in favour for HA (95% confidence interval (CI) −23.84 to −1.22.	**HA vs Placebo (Saline)** At three months (two studies: Cohen 2008 and DeGroot 2012; 92 participants) compared to control the total AOS score was 2.26 points lower (MD) (95% CI −11.23 to 6.72)	**HA vs Placebo (Saline)** At six months, two studies: Cohen 2008 and Salk 2006; 45 participants) compared to control, the AOS total score was 12.53 points lower (MD) in favour of HA (95% CI −23.84 to −1.22).
		-	**HA injection vs exercise therapy** **(Karatosun 2008)** Decrease in pain (endpoint 12 months) (MD −0.70, 95% CI −2.54 to 1.14)	-	**HA injection vs exercise therapy** **(Karatosun 2008)** At 12 months compared to exercise the AOFAS score was 13.10 points higher (MD) in favour of hyaluronic acid (95% CI 2.97 to 23.23)
		HA injection with different doses (Witteveen 2010) None of the VAS-scores for 'pain during walking activities decreased significantly at week 15.	-	-	-
Chang et al. (2013) / Systematic Review and Meta-analysis	4 RCTs, 1 double arm comparative and 4 single arm prospective studies were included in the meta-analysis	Across all the studies considered, regardless of their design, the combined effect size for measuring improvements in scores, focusing mainly on Ankle Osteoarthritis Scale (AOS) and Visual Analog Scale (VAS) from the baseline, was calculated at 2.01 (with a 95% confidence interval [CI] of 1.27 to 2.75) using a random-effect model due to significant differences among the trials ($I2 = 92.1\%$, $P < .0001$). Subsequent subgroup analysis showed that the effect size from randomised controlled trials was similar to that of single-arm prospective studies, with respective values of 2.33 (95% CI, 0.53 to 4.14) and 1.31 (95% CI, 0.59 to 2.03). In comparisons between the effectiveness of intra-articular hyaluronic acid (IAHA) and other treatments, particularly focusing on AOS and VAS, the combined effect size across five studies with comparative designs was found to be 0.85 (95% CI, -0.13 to 1.83). Further subgroup analysis of three double-blind and randomised controlled trials using saline as a reference therapy revealed a combined effect size of 1.00 (95% CI, -0.87 to 2.87).			

8.0 RESULT

This section focuses the results concerning safety, economic implication, and organisational aspects related to the disorders reviewed, including osteoarthritis.

8.1 SAFETY

8.1.1 DISORDERS OF THE SPINE, SHOULDER, HIP, KNEE AND ANKLE

(a) Adverse events

- **Spine**

The HA-CMC solution was selected due to its approval by the Korean Food and Drug Administration as the only HA solution permitted for use in the spine. Both RCTs reviewed reported no adverse events of the procedure.[24, 25]

- **Shoulder**

  - **Rotator cuff tears**

No serious adverse events or complications were observed during the studies.[21,32] Elderly patients with rotator cuff pathology exhibited good tolerance to HA infiltration.[32] Nevertheless, a mild vagal reaction was reported in 3% of study participants, and persistent pain at the injection site (ranging from 1-3% of study participants) were observed, both of which were associated with the HA injection.[21]

  - **Adhesive shoulder capsulitis (Frozen shoulder)**

One systematic review comprising seven studies found no adverse events or complication following injection in all studies. Only one study documented that 12 patient's experienced pain during capsular distension after the procedure, but not during the injection itself.[22]

  - **Shoulder tendinopathies**

The findings from the clinical trials involving patients with rotator cuff tendinopathy indicated that both subacromial HA injection and physiotherapy were well-tolerated, with no reported adverse events by participants or identified by

investigators in either group.[26-28] Notably, in the HA injection group, patients received HMW-HA exhibited significant induration at the injection site (p=0.007), and signs of inflammation at the site of injection were more in the HMW-HA group compared to the LMW-HA group (p=0.103; odds = 0.259).[27] However, those in the LMW-HA group demonstrated greater tolerance to injection pain.[27] In cases of supraspinatus tendinitis and tendinosis, whether treated with IAHA or periarticular injection, respectively, no adverse events or complications were reported.[29, 30] These findings collectively support the safety and tolerability of HA injections and physiotherapy in the management of rotator cuff tendinopathy and related conditions.

- **Knee**

  - **Knee/patellar tendinopathy**

    The current evidence regarding the safety of IAHA injections for patellar tendinopathy is overall positive across the four major clinical studies identified. None of the studies reported any serious adverse events related to the IAHA injections.[33-36] The most commonly reported side effects were mild, transient injection site reactions like pain, swelling or discomfort. The symptoms were self-limited and patients recovered within a few days without interventions.

    There were no cases of tendon rupture, ligament injury, infection, or other serious safety issues linked to IAHA reported in these studies of patients with patellar tendinopathy. This safety profile appears comparable to the well-established safety record of IAHA injections for knee osteoarthritis from large observational studies and surveillance data.

  - **Knee/patellar chondropathy**

    IAHA did not result in any reported adverse events in either of the studies, confirming its safety profile.

  - **Knee meniscus/ligament**

    Mao B et al. (2023) discovered no elevated likelihood of adverse events associated with IAHA compared to control groups across eight randomised controlled trials (p=0.06).[39] In the same vein, Tripathy SK et al. (2022) indicated that among the four studies they reviewed, there were no reported complications linked to IAHA.[40] Both studies concur that IAHA injections are safe for knee-related conditions.

- **Ankle**

  - **Ankle Tendinopathies**

    IAHA injections are well tolerated with a low risk profile. The most common adverse events are mild, transient swelling, pain or stiffness in the injected joint in 20.59% of patients,[35] none of which were serious or related to the safety product. More severe reactions are very rare. There are no major safety concerns identified from trials and surveillance data.

(b) Safety profile

The United States Food and Drug Administration (US FDA) 2021 safety profile on hyaluronic acid included a review of 39 studies. Among these, 36 studies focused on viscosupplementation, which involved the intra-articular injection of hyaluronic acid. Out of the total, 26 studies addressed knee treatments, four studies addressed on hips, and two each addressed hands, ankles, shoulders, and temporomandibular joint (TMJ) disorders. Additionally, three studies examined the use of HA as cartilage scaffolds. Local responses such as swelling, pain at injection site, arthralgia/joint pain, and effusion were frequently reported, with moderate to low-quality evidence. Joint stiffness, musculoskeletal pain, post-injection pain, pain flare ups and oedema were also common, but with lower-quality of evidence. Systemic reactions were documented in knees, shoulders, and TMJ disorders. A systematic review identified 63 fatalities related to knee viscosupplementation, with eight (12%) fatalities were categorised as possibly related to the IAHA, although causality could not be definitively determined. Skin reaction like rashes and peeling, were directly attributed to knee viscosupplementation in two studies.[62]

8.1.2 OSTEOARTHRITIS OF THE SHOULDER, HIP, KNEE AND ANKLE

(a) Adverse events

- **Glenohumeral osteoarthritis**

In the systematic review and meta-analysis conducted by Familiari F et al. (2023), only one single-arm open-label HA trial comprised 33 participants who received two HA injections reported that no significant adverse effects were observed throughout the study.[44]

In another systematic review by Zhang B et al. (2019), adverse events were documented in 13 studies following IAHA administration. The pooled adverse event rate was found to be 33.92% (406 out of 1197), with a serious adverse event rate of

5.35% (64 out of 1197). Common adverse events included musculoskeletal pain, headache, pain at injection site, diarrhoea, and flu-like symptoms. Serious adverse events included severe musculoskeletal pain, abscess, chest pain, and occurrences of cancer. Similar findings were observed in control groups receiving intra-articular injection of corticosteroids or phosphate-buffered saline. The reported pooled adverse event rate was 48.88% (240 out of 491) with a serious adverse event rate of 2.24% (11 out of 491). Common adverse events in the control group comprised rash, local effusion, pain at injection site, and musculoskeletal pain.[45]

An RCTs involving 290 patients investigated the safety of intra-articular DF-HA compared to a placebo in individuals with **osteoarthritis affecting the hip, ankle, shoulder, or elbow**. The study observed that the incidence of treatment-emergent adverse events (TEAE) after the initial injection, when considering all joints combined, was 49.3% in DF-HA group and 36.1% in the placebo group. No severe TEAEs were reported in either treatment group. However, among individuals who received DF-HA, serious TEAEs included ischaemic colitis in one participant with hip OA, cerebellar haemorrhage in one participant with shoulder OA, and radius fracture in one participants with elbow OA. Additionally, one participant with shoulder OA in the placebo group suffered from a subdural haematoma. All these TEAEs were considered moderate severity and showed improvement or resolved during the study. None were considered related to the study drug, and no TEAEs resulted in the discontinuation of treatment. Common TEAEs reported (occurring in more than 2% of subjects) included nasopharyngitis, injection site pain, nausea, palpitation, and arthralgia. In addition, there were no clinically significant changes observed between the DF-HA and placebo groups in terms of radiographic changes, manual joint examination, laboratory test results, and vital signs that could be considered as a TEAE.[46]

In another RCT consists of 77 patients comparing IAHA to triamcinolone hexacetonide, no serious adverse effects were reported. However, six patients (8.6%) experienced severe pain immediately after injection (four from the HA group and two from the triamcinolone group). No cases of infection were documented.[47]

Overall, the safety profile of intra-articular hyaluronic acid injections varies across studies (Table 11). The single-arm open-label HA trial found no significant adverse effects,[44] while a comprehensive systematic review reported a pooled adverse event rate of 33.92% with serious adverse events documented, including severe musculoskeletal pain, abscess, chest pain, and occurrences of cancer.[45] In the RCTs, the incidence of TEAE was 49.3% in the IA DF-HA, with no severe TEAEs. However, these events were considered of moderate severity, improved during the study, and were not attributed to the study drug.[46] In another RCT, no serious adverse effects were reported, but a small percentage experienced severe pain post-injection.[47] These findings highlight the need for careful consideration of the specific

HA formulation and patient characteristics/population when delivering IA HA treatments.

Table 11: The adverse events observed in the glenohumeral osteoarthritis studies

Study	No. of studies and participants	Outcome
Familiari F et al. (2023)	1 single-arm open-label HA clinical trial of 33 patients	No significant adverse effects
Zhang B et al. (2019)	13 studies (HA vs Phosphate buffered saline, corticosteroid)	Pooled adverse event rate of 33.92% (406 out of 1197) and a serious adverse event rate of 5.35% (64 out of 1197). • Common adverse events include musculoskeletal pain, headache, and pain at injection site, diarrhoea, and flu-like symptoms. • Serious adverse events include severe musculoskeletal pain, abscess, chest pain, and occurrences of cancer. • Similar findings were present in control groups receiving intra-articular injection of corticosteroids or phosphate-buffered saline, with a reported pooled adverse event rate of 48.88% (240 out of 491) and a serious adverse event rate of 2.24% (11 out of 491). • Common adverse events in the control group include rash, local effusion, pain at injection site, and musculoskeletal pain.

Kubo T et al. (2022)	1 RCT of 290 patients
	
	(DF-HA vs placebo)
		Incidence of TEAEs for all joints combined was 49.3% in DF-HA and 36.1% in placebo.
		
		• No severe TEAEs were reported in either treatment group.
		• Serious TEAEs in DF-HA group include:
		  ○ 1 ischemic colitis in hip OA
		  ○ 1 cerebellar haemorrhage in shoulder OA
		  ○ 1 radius fracture in elbow OA
		• Serious TEAEs in placebo group:
		  ○ 1 subdural hematoma in shoulder OA
		• Common TEAEs reported (>2% of subject) were nasopharyngitis, injection site pain, nausea, palpitation, and arthralgia.
		• No clinically significant between two groups in term of radiographic changes, manual joint examination, laboratory test results, and vital signs.

Tortato S et al. (2022)	1 RCT of 77 patients
	
	(HA vs Triamcinolone hexacetonide)
		No serious adverse effects has been reported.
		
		6 patients (8.6%) reported severe pain immediately after injection
		  ○ 4 patients (10.5%) from HA group and
		  ○ 2 (6.2%) from T group
		
		No cases of infection were reported.

HA: hyaluronic acid, DF-HA: diclofenac etalhyaluronate, TEAEs: treatment-emergent adverse events, RCT: randomised controlled trial

- **Hip osteoarthritis**

In a systematic review and meta-analysis by Wu YZ et al. (2021), the safety of viscosupplementation in hip OA was systematically evaluated. The rates of systemic adverse effects were uniformly low across all molecular weight groups, not exceeding 0.6% (RR: 0.006, 95% CI: 0.001 to 0.031). This suggests that, in terms of systemic adverse effects, viscosupplementation is generally considered safe. However, local adverse effects varied, with an overall rate of around 10%, except for the ultra-high-molecular-weight (UHMW) HA group, which exhibited a higher rate of 37.5% (RR: 3.75, 95% CI: 1.29 to 10.88). It's noteworthy that the variation in local adverse effects among different molecular weights was not statistically significant. While the overall safety of viscosupplementation is affirmed, the study emphasises the need for further research to comprehensively understand the differences in local adverse effects among different molecular weights of HA.[52]

Medina-Porqueres I et al. (2021) contributes insights from the safety perspective by focusing on PRP injections for hip OA. Notably, the PRP group showed a significantly higher post-injective pain reaction compared to the HA group in one study ($p = 0.043$). Despite this, the pain reaction was temporary and did not impact long-term results. Adverse events, including a superficial haematoma, were reported but did not have a significant long-term impact on results. The overall safety of PRP intra-articular injection for hip OA is acknowledged, with an understanding that the specific studies included in the systematic review may warrant further investigation for a comprehensive safety profile.[51]

Ali SE et al. (2021) delves into IAHA injections, emphasising that the overall risk ratio of complications between IAHA and control groups was not statistically significant (RR: 0.879, 95% CI: 0.527 to 1.466, p=0.622). Most reported complications were mild, including site infections, post-therapeutic pain, mild effusion, and local skin reactions. Importantly, no severe complications such as septic arthritis, femoral head collapse, or severe effusion were reported. The review concluded that IAHA injections provided pain relief and functional improvement without severe complications in the short term, aligning with the favourable safety profile observed in other studies.[50] Notably study by Leite VF et al. (2018) reveals that there is high evidence indicating that HA is not superior in terms of adverse events compared to placebo, as reflected in the risk ratio (RR) of 1.21 (95% CI, 0.79-1.86, P = 0.38). Importantly, high evidence supports the conclusion that HA is no different from methylprednisolone in terms of adverse events, with an RR of 1.21 (95% CI, 0.79-1.87, P = 0.38).[53]

Sambe HG et al. (2023) contributes to the safety discourse by highlighting that in four out of seven studies, no adverse events or complications were reported with IAHA injections for hip OA. Cases of post-injection pain were temporary and resolved

spontaneously. Notably, no major adverse events, such as infections or septic arthritis, were reported. The incidence of post-injection pain ranged from 3.22±2.40 to 3.50±2.22 on a 0-10 scale in the IAHA group, and no significant complications were noted, reinforcing the safety profile of IAHA for hip OA.[49] Belk JW et al. (2022), however, do not provide any information specific to the safety of PRP versus hyaluronic acid for the treatment of osteoarthritis of the hip.[48]

In summary, the synthesis of safety information from these systematic reviews affirms the overall safety of IAHA for hip OA. Systemic adverse effects are minimal, and while local adverse effects exist, they are generally mild and manageable. The collective evidence encourages the consideration of IAHA as a safe intervention for hip OA, with the understanding that ongoing research can further refine our knowledge of its safety profile.

- **Knee osteoarthritis**

Xue Y et al. (2023) reported 10 cases of adverse reactions to IA PRGF injection comprising one case of joint swelling and nine cases of stiffness and heaviness post-injection. Intra-articular HA caused joint swelling and stiffness in three cases. Additionally, 15 patients developed mild synovitis one week after IA PRP.[54]

In the meta-analysis by Tan J et al. (2020), adverse events were recorded across 20 studies involving 1,908 patients. The analysis revealed no significant difference in adverse events between the PRP and HA groups (RR 1.21, 95% CI 0.95 to 1.54; p=0.13), with mostly mild pain and swelling were reported. Additionally, eight cases of stiffness and heaviness were documented, along with two cases of pseudoseptic reactions.[58] The findings for knee OA, as presented in Table 12.

Table 12: The adverse events observed in the knee osteoarthritis studies

Study	No. of studies and participants	Outcome
Xue Y et al. (2023)	A network meta-analysis of 16 RCTs with 1,652 participants	10 cases of AE to intra-articular PRGF • 1 case of joint swelling • 9 cases of stiffness and heaviness after injection 3 cases of AE to intra-articular HA • joint swelling and stiffness 15 cases of AE to intra-articular PRP (one week after injection) • mild synovitis
Tan J et al. (2021)	A meta-analysis of 26 RCTs with 2,430 participants.	20 trials recorded adverse events including 1,908 participants. PRP adverse events = 109 out of 970 participants HA adverse events = 84 out of 938 participants Majority (64/83) had mild pain and swelling. 8 cases of stiffness and heaviness. 2 cases of pseudoseptic reactions.

In conclusion, findings from both studies highlighted the occurrence of adverse events associated with intra-articular injections, particularly involving PRP and HA. Xue Y et al. reported cases of joint swelling, stiffness following HA injection, while Tan et al. meta-analysis found comparable rates of adverse events between PRP and HA groups, predominantly mild pain and swelling. These results indicated the importance of vigilance in monitoring patients undergoing such treatments for potential adverse reactions.

- **Ankle osteoarthritis**

Safety evaluations across three systematic reviews revealed generally mild adverse events associated with intra-articular hyaluronic acid (IAHA) injections for ankle osteoarthritis. In Chang et al. (2013), among 285 participants receiving IAHA, 15% experienced adverse effects, primarily transient post-injection pain. Other adverse events included ankle effusion, inguinal lymph node enlargement, and local pruritus, all of which resolved spontaneously without specific treatment. In Witteveen et al. (2015), adverse events were infrequent across various comparisons, with no serious adverse events noted. However, the evidence was inconclusive due to small sample sizes and wide confidence intervals. In Paget et al. (2023), no severe or systemic adverse events were reported, with the most common adverse events being mild pain and local swelling at the injection site. These events were generally transient and resolved without medical intervention. Overall, while some adverse events were reported, they were mostly mild and temporary, indicating a favourable safety profile for IAHA in the treatment of ankle osteoarthritis.

8.2 ECONOMIC IMPLICATION

There was no retrievable evidence regarding the cost-effectiveness of IAHA concerning the disorders under review. Nevertheless, a retrospective study and a clinical practice guidelines highlighted the health care cost associated with rotator cuff repair.

Shoulder: Rotator Cuff Repair

In a retrospective study by Malik AT et al. (2020), national insurance claims data was analysed to examine **health care costs in the year preceding elective arthroscopic rotator cuff repair (RCR)**. The study, using the Humana Administrative Claims (HAC) dataset from 2007 to 2015, focused on patients undergoing RCR for degenerative rotator cuff tears within one year before surgery across the United States. The cohort was categorised into Medicare Advantage (MA) or commercial insurance plans, comprising 24,987 patients: 73.9% (18,457) were MA beneficiaries and 26.1% (6,530) were commercial beneficiaries. Pre-operative costs totalled US$16,923,595 ($916 per patient) for MA beneficiaries and $8,397,291 ($1,285 per patient) for commercial beneficiaries. Key contributors to RCR-related health care costs were MRI scans (36% MA, 56% commercial) and office visits (25% MA, 17% commercial). Per-patient average reimbursements (PPARs) varied for each resource: office visits (MA $240, commercial $249), radiographs (MA $60, commercial $93), MRI scans (MA $385, commercial $813), CT scans (MA $223, commercial $562), steroid injections (MA $97, commercial $137), **HA injections (MA $422, commercial $602)**, physical therapy (MA $473, commercial $551), and pain medications (MA $208, commercial $136). Pain medications (opioids and NSAIDs) and steroid injections were notably utilised in the three months preceding surgery, with HA injections administered to less than 1% of patients.[63]

Weber and Chahal (2020) highlighted that the societal expenses linked to a medical condition include both direct and indirect costs. Direct costs pertain to expenses related to diagnosis and treatment, while indirect costs involve lost income due to inability to work or reduced wages, as well as missed workdays and disability payments. In the United States, approximately 250,000 rotator cuff repairs ($6,367 per medical patient) are performed annually. Despite the high cost, rotator cuff repair results in an increase in quality-adjusted life-years for all patients, regardless of age. The analysis revealed an estimated annual societal saving of $3,442,750,000 over lifetime of patients who undergo the 250,000 yearly rotator cuff repairs in the United States.[12]

8.3 ORGANISATIONAL

8.3.1 Length of follow-up

The follow-up period in the studies varied from one week to five years. For spinal disorders, these periods were classified as short-term at 2 weeks, mid-term at 6 weeks, and long-term at 12 weeks. In other joint disorders and osteoarthritis, the period were categorised as short-term ranging from 3 to 6 weeks, mid-term at 12 weeks, and long term at or beyond 6 months .

8.3.2 Patient satisfaction

Patient satisfaction was addressed in only two studies. In one study focusing on supraspinatus tendinosis, at 12 weeks, 89% of individuals in the HA group reported satisfaction with the treatment, although this percentage decreased to 68% at 24 weeks and after one year.[30] Satisfaction rates were analysed in four studies within a meta-analysis involving adults with knee osteoarthritis, which showed no significant difference between PRP and HA groups.[58] Overall, from the studies reviewed, the observed effects included pain reduction, improved functionality, and consequently an enhancement in overall quality of life.

8.3.3 Facility, administration technique/strategy and clinician expertise

The primary method employed for IA injection involved image-guided techniques (including ultrasound or fluoroscopy guidance), followed by blind techniques via anatomical guidance, or a combination of both. Intra-articular injection procedures for the shoulder mainly utilised a posterior approach, subsequently by an anterior method.

The IAHA procedure is administered in an outpatient settings and performed by skilled practitioners, including physicians, surgeons, or orthopaedic specialists, with some having experience ranging from 10 to 20 years.[24- 28, 31, 46, 47]

8.3.4 Registration

The hyaluronic acid injection is registered with Medical Device Authority, Ministry of Health Malaysia. These injections are approved for treating osteoarthritis pain, primarily in the knee joint, as well as in other synovial joints including the hip, fingers, toes, ankle, shoulder, elbow, temporomandibular, and facet joints. They are intended for patients who have not responded adequately to conservative non-pharmacologic therapy and simple analgesics, or when other treatments (analgesics, NSAIDs, physical therapy) are inadequate or contraindicated. Additionally, these injections are used for long-term restoration of joint lubrication, pain reduction, and mobility improvement in degenerative

or post-traumatic joint diseases. The use of these products is restricted to legally approved practitioners, preferably rheumatologists, orthopaedic surgeons, and sports medicine doctors.[64]

8.3.5 Guidelines

The American Academy of Orthopaedic Surgeons, in its 2013 proposed criteria for the use of optimal management of total rotator cuff tears, states that the recommended non-surgical treatment of rotator cuff injuries consists of five main areas: pharmacotherapy and corticosteroid injections, information about symptom control, activity level adjustment, home training and prognosis, manipulative therapy, functional training and physiotherapy. Among them, injection therapy is one of the commonly used conservative treatments. Current injection therapies for rotator cuff injuries include corticosteroid, PRP, hyaluronic acid, and prolotherapy therapy.[13] Table 16 summarised the recommendations derived from clinical practice guidelines (CPG) and systematic reviews of CPGs pertaining to intra-articular injections of HA, corticosteroid, and PRP.

Table 16: Intra-articular Injection Recommendations – International and Local Guidelines, and Systematic Review of Clinical Practice Guidelines Findings

Guidelines / Study	Disorder(s)	Recommendations
Rotator cuff injuries		
American Academy of Orthopaedic Surgeons Management of Rotator Cuff Injuries: Evidence-based Clinical Practice Guideline (2019)[65]	Shoulder	Hyaluronic Acid Injections for Rotator Cuff Tears: **Limited evidence** supports the use of hyaluronic acid injections in the nonsurgical management of patients with rotator cuff pathology. Implication: Practitioners should feel little constraint in following a recommendation labeled as limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harms. Patient preference should have a substantial influencing role. Corticosteroid Injections for Rotator Cuff Tears: **Moderate evidence** supports the use of a single injection of corticosteroid with local anaesthetic for short-term improvement in both pain and function for patients with shoulder pain.
Osteoarthritis		
American Academy of Orthopaedic Surgeons Management of Glenohumeral Joint Osteoarthritis: Evidence-Based Clinical Practice Guideline (2020)[66]	Shoulder OA	Strong evidence supports that there is no benefit to the use of hyaluronic acid in the treatment of glenohumeral joint osteoarthritis. (Strength of recommendation: Strong)

Guidelines / Study	Disorder(s)	Recommendations
American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Hip: Evidence-Based Clinical Practice Guidelines (2023)[67]	Hip OA	**Intra-articular hyaluronic acid** should not be considered for treatment of symptomatic osteoarthritis of the hip as it does not improve function or reduce pain better than placebo. (Strength of recommendation: Strong) **Intra-articular corticosteroid** could be considered to improve function and reduce pain the short-term for patients with symptomatic osteoarthritis of the hip (Strength of recommendation: Moderate)
American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Knee (Non-Arthroplasty) (3rd Edition): Evidence-Based Clinical Practice Guideline (2021)[68]	Knee OA	**Hyaluronic acid intra-articular injection(s)** is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee. (Strength of recommendation: Moderate) **Intra-articular corticosteroids** could provide short-term relief for patients with symptomatic osteoarthiritis of the knee. (Strength of recommendation: Moderate) **Platelet-rich plasma (PRP)** may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee. (Strength of recommendation: Limited)
National Institute for Health and Care Excellence (NICE) Guidelines Osteoarthritis in over 16s: diagnosis and management (2022)[69]	OA	Do not offer **intra-articular hyaluronan injections** to manage osteoarthritis. Consider **intra-articular corticosteroid injections** for short-term relief (2 to 10 weeks) when other pharmacological treatments are ineffective or unsuitable, or to support therapeutic exercise.
Malaysian Clinical Practice Guidelines Management of Osteoarthritis (Second Edition) (2013)[70]	OA	The CPG is unable to recommend the use of viscosupplementation in the treatment of osteoarthritis due to a lack supporting evidence.
Gibbs AJ et al.[71] SR of Clinical Practice Guidelines (25 CPGs)	Hip and Knee OA	Intra-articular injection recommendations varied. **Hip and knee recommendations:** • PRP: No guidelines recommended PRP for hip or knee OA. • Stem cell injections: strongly recommended against. **Hip-specific recommendations:** • Divergent for corticosteroids: 3 recommended, 1 conditionally recommended against. • Hyaluronic acid: recommended against (all 4 CPG). **Knee-specific recommendation:** • Corticosteroid: recommended for use (all 4 CPG). • Hyaluronic acid: 3 against, 1 conditionally recommended for.

Guidelines / Study	Disorder(s)	Recommendations
Phillips M et al.[72] SR of CPG (27 CPGs)	Knee OA	**Intra-articular hyaluronic acid** • 10 (37.0%) strong recommendations for use. • 10 (37.0%) conditional recommendations for use. • 2 (7.4%) uncertain recommendations. • 2 (7.4%) weak recommendations against. • 3 (11.1%) strong recommendations against. **Intra-articular corticosteroid** • 10 (41.7%) strong recommendations for use. • 11 (45.8%) conditional recommendations for. • 2 (8.3%) uncertain recommendations. • 1 (4.2%) strong recommendation against. **Platelet-rich plasma** • 9 (81.8%) uncertain or unable to make a conclusive recommendation for or against. • 2 (18.2%) recommended against.
Sabha M and Hochberg MC.[73] Comparison of the 2019 American College of Rheumatology/Arthritis Foundation (ACR/AF), the 2019 Osteoarthritis Research Society International (OARSI), and the 2020 Veterans Affairs and Department of Defence (VA/DoD) treatment guidelines.	Hip and Knee OA	**Intra-articular hyaluronic acid:** Hip OA: not recommend by the ACR/AF and OARSI KneeOA: conditionally recommended for use by OARSI and VA/DoD. ACR/AF: • IA HA conditionally recommends against. OARSI: • IA HA conditionally recommended for knee OA, conditionally recommend against for hip OA. VA/DoD: • consider IA viscosupplementation injections for knee OA for patients with persistent symptoms despite first-line therapy. **Intra-articular steroid injection:** recommended among all three guidelines for first-line therapies. ACR/AF: • IA CS recommended for hip and knee OA with ultrasound guidance. • Strongly against glucosamine, chondroitin sulfate products, and PRP injection. OARSI: • IA CS for knee and hip OA who fail to respond or cannot receive the first-line therapies. • Strongly against glucosamine, chondroitin sulfate products. VA/DoD: • IA CS for knee and hip OA (with ultrasound guidance FfolloFfor hip) when first-line therapies fail or become inadequate.

In a document received from the requestor, Aetna group of companies, including Aetna Life Insurance Company and its affiliates in the United States, addresses viscosupplementation for commercial medical plans in their Clinical Policy Bulletins No. 0179. Precertification of viscosupplementation products is required of all Aetna participating providers and members under applicable plan designs.[74]

I. Criteria for Initial Approval

Aetna considers viscosupplementation (hyaluronates) medically necessary for the treatment of osteoarthritis (OA) in the knee **when all of the following criteria are met:**

A. The diagnosis is supported by radiographic evidence of osteoarthritis of the knee (e.g., as joint space narrowing, subchondral sclerosis, osteophytes and sub-chondral cysts) or the member has at least five of the following signs and symptoms:
    1. Bony enlargement
    2. Bony tenderness
    3. Crepitus (noisy, grating sound) on active motion
    4. Erythrocyte sedimentation rate (ESR) less than 40 mm/hr
    5. Less than 30 minutes of morning stiffness
    6. No palpable warmth of synovium
    7. Over 50 years of age
    8. Rheumatoid factor less than 1:40 titer (agglutination method)
    9. Synovial fluid signs (clear fluid of normal viscosity and WBC less than 2000/mm3); **and**

B. The member has knee pain which interferes with functional activities (e.g., ambulation, prolonged standing); **and**
C. The member has experienced an inadequate response or adverse effects with non-pharmacologic treatment options (e.g., physical therapy, regular exercise, insoles, knee bracing, weight reduction); **and**
D. The member has experienced an inadequate response or intolerance or has a contraindication to a trial of an analgesic (e.g., acetaminophen up to 3 to 4 grams per day, non-steroidal anti-inflammatory drugs [NSAIDs], topical capsaicin cream) for at least 3 months; **and**
E. The member has experienced an inadequate response or intolerance or has a contraindication to a trial of intraarticular steroid injections for at least 3 months; **and**
F. The member is not scheduled to undergo a total knee replacement within 6 months of starting treatment.

Aetna considers all other indications as experimental, investigational, or unproven.

II. Continuation of Therapy

Aetna considers continuation of viscosupplement therapy medically necessary for treatment of osteoarthritis in knee **when all of the following criteria are met:**

A. Member meets all initial medical necessity criteria; **and**
B. Member has experienced improvement in pain and functional capacity following the previous injections; **and**
C. At least 6 months has elapsed since the last injection in the prior completed series of injections.

The FDA-approved dosing recommendations for the treatments of osteoarthritis in the knee were also included. This Clinical Policy Bulletins is subject to updates and changes. The most recent update was on April 9, 2024.[73]

In summary, recommendations regarding the use of intra-articular treatments for various joint conditions vary across guidelines and studies. **Hyaluronic acid injections show limited or no benefit for rotator cuff tears, glenohumeral joint osteoarthritis, and osteoarthritis of the hip and knee** according to multiple guidelines and studies. In contrast, corticosteroid injections are consistently recommended as a first-line therapy for shoulder pain and osteoarthritis of the hip and knee.

Platelet-rich plasma injections have uncertain or inconclusive recommendations across studies, while stem cell injections are strongly discouraged. Patient preference and clinical judgment play significant roles in decision-making, particularly in the absence of clear-cut evidence for or against certain treatments.

In conclusion, while there is some variability in recommendations, intra-articular corticosteroid injections emerge as a commonly recommended treatment option for shoulder pain and osteoarthritis of the hip and knee. The limited efficacy and inconsistent recommendations for hyaluronic acid injections emphasised the need for further research and individualised patient care in the management of these conditions.

8.3.6 Hip osteoarthritis

The assessment of IAHA for hip OA extends beyond individual clinical practice guidelines to include recent systematic reviews and health technology assessment. These evaluations provide a comprehensive perspective on the organisational dimensions influencing the adoption of IAHA in hip OA management.

Aggregate Analytics, under contract with the Washington State Health Care Authority, meticulously evaluated the efficacy of IAHA for hip OA, relying on data from three fair-quality RCTs, all devoid of industry funding.

In the comparison between HA and placebo (saline), involving two RCTs encompassing a total of 426 participants, no appreciable differences emerged in function (assessed through WOMAC and Lequesne scores) or pain (Low Strength of Evidence, SOE). Notably, whether administered as a single 6ml injection or three 2ml injections, HA showed no statistical disparities against saline controls. Arthroplasty rates were 0% (0/38) for HA and 2.8% (1/36) for placebo, a statistically insignificant difference leading to an overall assessment of insufficiency in evidence. Adverse events were equally distributed across both groups.

In a separate comparison between HA and steroid injections (one RCT, also including a comparison with saline), the evidence was insufficient for all outcomes. The HA regimen comprised three 2ml injections, while the comparator, Depomedrol, involved a single 1ml injection.

Furthermore, in the context of HA versus platelet-rich plasma (PRP) in a single RCT involving 74 participants, the assessment revealed no significant differences in function or pain (Low SOE). Nevertheless, evidence regarding safety was deemed insufficient.

In conclusion, the numeric information from these studies underscores the current state of uncertainty and insufficiency in available data. While the evidence does not strongly support the efficacy of IAHA for hip OA, it accentuates the need for further research, potentially addressing variations in injection protocols and patient profiles, to establish a clearer understanding of the effectiveness and safety of IAHA in managing hip osteoarthritis.

9.0 LIMITATIONS

Certain limitations of this review warrant acknowledgement and should be taken into consideration when interpreting the findings. The selection and evaluation of the studies were conducted separately by individual independent reviewers for upper limbs and lower limbs disorders. Although there was no restriction in language during search, only full text articles in English published in peer-reviewed journal were included in the report, which potentially excluding relevant articles and further limiting the number of studies included. Additionally, many of the studies had small sample sizes, and variability in the follow-up periods. An increased heterogeneity was also observed among the studies, which can be attributed mainly to the treatment protocol that has not been standardised. Furthermore, the primary outcome measures relied on subjective assessments (such as pain, joint functionality and range of movement) utilising different types of validated assessment tools.

10.0 DISCUSSION AND CONCLUSION

Spinal disorders

In spinal disorders management, two studies have indicated that hyaluronic acid-carboxymethylcellulose (HA-CMC) solution could serve as an alternative to corticosteroid in selective nerve root block (SNRB) for conditions such as spinal stenosis and lumbar radiculopathy. Patients who received HA-CMC injection demonstrated comparable effects in reducing pain, improving functionality, and enhancing overall quality of life. However, it is essential to interpret these results with caution due to single study for each disorder and small sample size. The observed benefits are minimal, and HA-CMC should not be used until better-quality evidence is available. As of this review, hyaluronic acid has not been approved for spinal injection by the MDA Malaysia.

Shoulder disorders

The findings across various shoulder conditions highlights the effectiveness of hyaluronic acid injections as a valuable therapeutic option. For **rotator cuff tears**, HA injections demonstrated notable pain reduction, improved shoulder function, and enhanced quality of life in the short term, especially when combined with rehabilitative treatment. However, the duration of these benefits is limited to less than six months, contrasting with platelet-rich plasma injections, which may provide favourable long-term outcomes beyond six months. In cases of **adhesive shoulder capsulitis** (frozen shoulder), HA injections exhibit short-term benefits, comparable to corticosteroid injections and other non-surgical treatments, emphasising their potential role in early mobilisation and preventing shoulder immobilisation when combined with physiotherapy. Regarding **rotator cuff tendinopathy**, HA injection did not demonstrate a significant difference in pain reduction and functional improvement compared to placebo, both

in the short-term and long-term. In contrast, corticosteroid injections are effective in the short-term, while PRP and prolotherapy offer better long-term outcomes. Low molecular-weight HA emerges as a promising option, particularly in the initial three months, providing successful pain relief for tendinopathy. However, cautious interpretation is advised due to the limited evidence for certain conditions, such as supraspinatus tendinitis and tendinosis, where findings are based on single studies with small populations. Overall, the integration of HA injections into comprehensive treatment approaches demonstrates promising results. Nevertheless, further research especially through randomised controlled trials, is needed to establish optimal dosages and long-term effectiveness across different shoulder conditions.

Knee Disorders

The available evidence indicates the potential use of HA injections to alleviate short-term pain in knee disorders unrelated to osteoarthritis, particularly in cases of tendinopathies and chondral injuries. Various randomised trials have revealed significant improvements in pain scores with HA injections compared to control treatments during follow-ups spanning 1-6 months. However, the consistency of benefits for long-term pain relief and functional enhancements remains uncertain. While some studies demonstrate prolonged benefits for up to 1-2 years, others show no notable differences versus controls beyond the initial short-term improvements. Recent systematic reviews examining IAHA in ACL reconstruction and meniscectomy procedures have failed to present clear advantages in pain relief or functionality.

Hyaluronic acid injections are consistently regarded as safe across the assessed conditions, displaying a low incidence of adverse events similar to control injections or interventions. This safety profile supports the potential utilisation of HA, despite the variability and brief duration of observed benefits.

To summarise, considering its favourable safety profile, HA injection may be considered for short-term pain relief in multimodal knee rehabilitation protocols addressing tendinopathies and cartilage injuries. Nevertheless, further high-quality evidence is essential to decisively determine long-term effects, functional improvements, ideal dosing schedules, and identify patient subgroups most likely to benefit sustainably. Ongoing assessments in robust comparative effectiveness trials comparing HA with alternative injectable therapies will provide clarity regarding its appropriate role in managing non-osteoarthritic knee pathologies.

Ankle Tendinopathies

Low quality evidence suggests HA injection results in small, short-term improvements in pain and function compared to placebo or ESWT for ankle tendinopathies. However, benefits are unlikely to be sustained long-term. Hyaluronic acid injection appears safe but cost-effectiveness is unknown. Additional high-quality, sufficiently powered RCTs with low risk of bias and longer follow-up are warranted to guide clinical practice.

Osteoarthritis

The available evidence on **glenohumeral OA** suggest that IAHA may effectively reduce pain and improves shoulder function compared to baseline. Combining physical therapy with HA injection demonstrated superior pain relief. However, the control group, which received IA corticosteroid or triamcinolone injections or placebo, also exhibits clinical improvements, indicating a potential placebo effect with IA shoulder injection. No significant difference were noted in the improvement of shoulder range of motion. Nevertheless, IAHA yields better and longer-lasting outcomes, up to 6 months, particularly those with mild to moderate osteoarthritis. The technique of IA injection varied, primarily utilising image-guided methods, with skilled clinicians administering injections. The safety profile of IAHA injection differed among studies with varying rates of adverse events, indicating a cautious usage of HA formulation.

In consolidating insights from diverse sources, the conclusion regarding IAHA for **hip OA** leans towards caution and prudence, with a nuanced inclination away from endorsing its widespread use. The study by Leite et al. (2018) underscores the limited evidence supporting IAHA's superiority over placebo in pain relief at 3 months, emphasising a modest impact on patient outcomes. This aligns with the stance of esteemed organisations such as the American College of Rheumatology (ACR) and the Veterans Affairs/Department of Defense, both of which express reservations and discourage IAHA use in hip OA. The systematic reviews and meta-analyses conducted by Belk et al. (2022), Ali et al. (2021), Sambe et al. (2023), Ivan Medina-Porqueres et al. (2021), and Wu et al. (2021) collectively contribute to a narrative that lacks consistent evidence favouring IAHA, particularly when compared to alternatives such as PRP. Variable outcomes in pain reduction and functional improvement, coupled with methodological heterogeneity, add layers of uncertainty to the overall efficacy of IAHA.

Given this landscape, policymakers are urged to adopt a cautious and measured stance, recognising the prevailing uncertainties and the absence of resounding support for IAHA. While acknowledging the potential benefits for specific patient populations, a more conservative approach would involve refraining from widespread endorsement until further robust evidence emerges. Further high-quality research, addressing the gaps in the current evidence, is imperative to elucidate the true efficacy, safety, and optimal utilisation of IAHA in the management of hip OA, thereby informing evidence-based clinical practices. Policymakers may consider advocating for additional high-quality research to address existing gaps, ensuring that decisions align with the principles of safety, efficacy, and patient-centered care.

Across the studies on **knee OA,** PRP injection demonstrated the effectiveness as a superior non-surgical treatment option compared to hyaluronic acid in functional improvement and pain relief. Combination therapies with PRP were found to be more effective than monotherapy, with sustained pain relief up to a year exceeding HA treatments. HA treatments had varied results with the maximum improvement occurred for short-term. HA provides good short-term relief but lacks the longevity offered by PRP injections. PRP injections were able to sustain pain relief and functional improvement for the long-term. There is no clear distinction between types of PRP superiority. The safety profiles of PRP are comparable to HA injections. However, it is

noteworthy that across clinical practice guidelines, recommendations regarding PRP injections remain uncertain or inconclusive.

Based on the comprehensive evaluation of the available evidence regarding the effectiveness and safety of HA injections for **ankle OA**, several key findings emerge. The effectiveness of HA injections for ankle OA remains uncertain, with mixed results reported across systematic reviews. While some studies suggest potential benefits in terms of pain reduction and functional improvement, particularly in comparison to placebo or exercise therapy, others fail to demonstrate clinically significant differences between HA and comparator treatments. Additionally, the evidence is limited by heterogeneity in study designs, outcome measures, and patient populations, making it challenging to draw definitive conclusions regarding the efficacy of HA for ankle OA.

Overall, HA injections appear to have a favourable safety profile for the treatment of ankle OA. Adverse events reported across studies were generally mild and transient, with no serious adverse events reported. Common adverse events included post-injection pain and local swelling, which resolved spontaneously without the need for medical intervention. While some variability in adverse event reporting exists between studies, the overall incidence of adverse events appears to be low.

In conclusion, the evidence regarding the effectiveness of HA injections for ankle OA is inconclusive, with conflicting results and methodological limitations undermining the strength of available evidence. While HA injections may offer some potential benefits in terms of pain reduction and functional improvement, further high-quality research, including large-scale randomised controlled trials with standardised outcome measures and longer follow-up periods, is needed to elucidate the true efficacy of HA for ankle OA. Nevertheless, the favourable safety profile observed across studies suggests that HA injections may be a reasonable treatment option for patients with ankle OA, particularly in those who have failed conservative therapies or are unable to undergo surgical interventions.

Conclusion

In summary, HA injections are effective in reducing pain, improving functionality, increasing range of motion, and enhancing quality of life, for conditions such as rotator cuff tears and adhesive shoulder capsulitis, knee disorders associated with tendinopathies and chondral injuries, ankle tendinopathies, and mild to moderate glenohumeral osteoarthritis, especially when combined with rehabilitation. However, these benefits are short-term, lasting less than six months, and are not sustained long-term (beyond six months) post-intervention. Compared to alternatives like PRP, HA injection is less effective in the long-term. Evidence for HA injection in rotator cuff tendinopathy is limited and inconsistent, indicating the need for further robust trials to determine optimal use and long-term benefits.

Hyaluronic acid-carboxymethylcellulose (HA-CMC) shows potential as an alternative to corticosteroids in selective nerve root block (SNRB) for spinal stenosis and lumbar

radiculopathy. However, the benefits are minimal due to limited studies and small sample sizes, requiring further high-quality research before recommending its use.

For knee OA, HA treatments provide good short-term relief but lack the long-term effectiveness offered by PRP injections. PRP injections were able to sustain pain relief and functional improvement for the long-term.

Hyaluronic acid injection yields no effectiveness for conditions of knee meniscus or ligament injury, hip osteoarthritis, and ankle osteoarthritis. Throughout the literature reviewed, there is inadequate strong evidence available to establish the superiority of HA over other treatments such as corticosteroids, physiotherapy, or other conservative management approaches. Further high-quality research is needed to determine the long-term benefits and to guide clinical practice.

Recommendations regarding HA treatments vary across guidelines, with evidence suggesting limited or no benefit for conditions such as rotator cuff tears, glenohumeral joint osteoarthritis, and osteoarthritis of the hip and knee. Hyaluronic acid injections are generally well-tolerated, with minimal incidence of serious adverse events. However, caution should be exercised in cases of glenohumeral osteoarthritis due to the potential risk of severe musculoskeletal pain, abscess formation, chest pain, and occurrences of malignancy. Given the diverse injection techniques required for different pathological conditions, it is advisable that these injection to be performed by practitioners with specialised skills and extensive experience.

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