

The Efficacy of Intra-articular Hyaluronic Acid Injections in Patients with Knee Osteoarthritis and Concomitant Vitamin D Deficiency: Literature Review

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Abstract

Knee osteoarthritis is a chronic degenerative joint disorder involving articular cartilage, subchondral bone, synovium, and periarticular structures. Intra-articular hyaluronic acid (IAHA) is widely used as a viscosupplementation therapy; however, its clinical effectiveness remains controversial with heterogeneous outcomes across studies. Vitamin D deficiency has been implicated in musculoskeletal dysfunction, inflammation, and oxidative stress, which may influence therapeutic response in osteoarthritis patients. This literature review aims to evaluate the effectiveness of intra-articular hyaluronic acid in patients with knee osteoarthritis and concomitant vitamin D deficiency or insufficiency based on recent evidence from 2021–2026. A systematic literature review was conducted using PubMed, PubMed Central, Google Scholar, ScienceDirect, Cochrane Library, BMJ, Frontiers, MDPI, and clinical guidelines. Eligible studies included randomized controlled trials, systematic reviews, meta-analyses, cohort studies, and consensus reports. Narrative synthesis was applied due to limited direct evidence evaluating combined IAHA and vitamin D intervention. Results of the study show that IAHA demonstrates small to moderate effects in reducing pain and improving functional outcomes in knee osteoarthritis, particularly in mild-to-moderate disease stages. However, pooled evidence suggests limited clinical superiority compared to placebo in several meta-analyses. Vitamin D deficiency is consistently associated with increased pain severity, reduced functional status, and lower quality of life. Emerging evidence indicates that vitamin D supplementation combined with IAHA may reduce synovial oxidative stress and improve clinical outcomes, although the evidence remains preliminary and non-conclusive. IAHA should not be recommended as a universal treatment for knee osteoarthritis. In patients with vitamin D deficiency or insufficiency, correction of vitamin D status may be considered as part of a multimodal approach and may enhance clinical response to IAHA. High-quality randomized controlled trials are required to confirm the synergistic effect.

Introduction

Knee osteoarthritis is one of the most common degenerative musculoskeletal diseases found in adults and the elderly worldwide. This condition is characterized by progressive damage to articular cartilage, changes in subchondral bone, and chronic inflammation of the synovial tissue, leading to pain, joint stiffness, limited mobility, and a reduced quality of life. Clinically, knee osteoarthritis impacts not only the physical but also the psychosocial aspects due to increasing limitations in daily activities as the disease progresses (Zhang et al., 2025; Giorgino et al., 2023; Du et al., 2023; Dima et al., 2025; Glinkowski & Tomaszewski, 2025).

Treatment for knee osteoarthritis is multidimensional, ranging from non-pharmacological therapies to pharmacological therapies and intra-articular interventions. One widely used therapy is intra-articular hyaluronic acid injection (IAHA), which aims to restore synovial fluid

viscoelasticity, improve joint lubrication, and reduce friction between articular surfaces. Theoretically, IAHA also has biological effects such as modulating inflammation and protecting against cartilage degradation (Brophy & Fillingham, 2022; Chen et al., 2021; Si et al., 2023; Ferkel et al., 2023; Glinkowski & Tomaszewski, 2025).

However, various literature indicates that the clinical effectiveness of IAHA remains controversial. Several meta-analyses report that the IAHA has only a small to moderate effect on reducing pain and improving joint function, while other studies show no significant difference compared to placebo. These differences in results indicate heterogeneity in clinical responses influenced by various factors such as the degree of osteoarthritis, the type of hyaluronic acid preparation, and patient characteristics (Migliorini et al., 2024a; Bruyère et al., 2025; Chavda et al., 2022; Vincent, 2021; Han et al., 2021; Miller et al., 2021).

In addition to local joint factors, osteoarthritis is also influenced by systemic factors, which have received increasing attention in recent years. One widely studied factor is vitamin D. Vitamin D not only plays a role in calcium metabolism and bone health, but also plays an important role in immune system regulation, inflammation modulation, and neuromuscular function. Vitamin D deficiency has been associated with increased musculoskeletal pain, decreased muscle strength, and a reduced quality of life in patients with knee osteoarthritis (Amirkhizi et al., 2022; Divjak et al., 2023; Saengsiwaritt et al., 2023; Georgescu et al., 2024; Iqhrammullah et al., 2026).

Several observational studies have shown that patients with low vitamin D levels tend to have higher pain scores and poorer joint function compared to patients with normal vitamin D levels. However, the results of vitamin D supplementation interventions have been inconsistent, so its role in osteoarthritis therapy remains uncertain (Annamalai et al., 2023; Wang et al., 2023a; Jin et al., 2022; Zuo et al., 2024; Wang et al., 2023b).

In this context, it is hypothesized that there is a potential interaction between IAHA and vitamin D status in determining the clinical response of patients with knee osteoarthritis. IAHA acts locally in the intra-articular environment by improving viscosity and modulating joint inflammation, while vitamin D acts systemically by regulating inflammation, bone metabolism, and muscle function. The combination of the two could theoretically provide a synergistic effect in improving symptoms and function in patients with knee osteoarthritis (Busa et al., 2023; Patnaik et al., 2023; Amirkhizi et al., 2022; Divjak et al., 2023).

However, to date, there is insufficient clinical evidence specifically evaluating the effectiveness of the combination of IAHA and vitamin D in patients with knee osteoarthritis. Most of the literature still addresses these two variables separately, leaving their interactive relationship unexplained. This creates a research gap that is important to further explore in order to develop more effective, evidence-based osteoarthritis therapies (Georgescu et al., 2024; Wang et al., 2023a; Jin et al., 2022; Glinkowski & Tomaszewski, 2025; Migliorini et al., 2025).

Based on this background, a comprehensive literature review is needed to evaluate the effectiveness of intra-articular hyaluronic acid in patients with knee osteoarthritis, considering vitamin D status as a biological factor potentially influencing clinical outcomes. This study is expected to contribute to the development of a more individual, rational, and evidence-based medicine approach to knee osteoarthritis therapy.

Method

Research Design

This research uses a literature review design with a systematic search approach. The literature review was chosen because the aim of the study was to synthesize the latest scientific evidence regarding the effectiveness of intra-articular HA injections in knee osteoarthritis patients with vitamin D deficiency or insufficiency, not to carry out direct intervention on research subjects. A systematic search approach was used so that the process of identification, selection and synthesis of literature was transparent. The reporting principles follow the main points of PRISMA 2020 in an adaptive manner, especially in the formulation of questions, inclusion-exclusion criteria, search strategies, and synthesis of results. However, because the number of direct primary studies is still limited and heterogeneous, the synthesis was carried out narratively, rather than quantitative meta-analysis. The main reference year limit is 2021-2026. Articles outside this range are not used as primary references, except when necessary for classical definitions or historical background. In this revised manuscript, the bibliography is arranged in Vancouver format and all main references are within the last five years.

PICO Formula

Table 1. PICO Formula

Component	Definition
Population	Adult patients with knee osteoarthritis who have vitamin D deficiency or insufficiency based on serum 25(OH)D levels.
Intervention	Intra-articular hyaluronic acid injections, either single or serial, with or without vitamin D supplementation.
Comparator	HA alone, placebo/saline, conservative therapy, intra-articular corticosteroids, or no vitamin D correction group.
Outcomes	Pain (VAS/NRS), function (WOMAC/KOOS/Lequesne), quality of life, biomarkers of oxidative stress/inflammation, analgesic requirements, and adverse events.
Study design	Randomized controlled trials, quasi-experimental studies, cohort studies, systematic reviews, meta-analyses, umbrella reviews, and clinical guidelines as supporting evidence.

Literature Search Strategy

A literature search was conducted through PubMed/MEDLINE, PubMed Central, Google Scholar, ScienceDirect, the Cochrane Library, BMJ, Frontiers, MDPI, and relevant clinical guideline sources. Keywords were compiled using free terms and relevant medical terms, then combined with the Boolean operators AND and OR.

Table 2. Literature Search Strategy

Database	Search string example
PubMed/MEDLINE	("knee osteoarthritis" OR "osteoarthritis of the knee") AND ("hyaluronic acid" OR hyaluronan OR viscosupplementation) AND ("vitamin D" OR "25- hydroxyvitamin D" OR deficiency OR insufficiency)
PubMed Central/Frontiers/BMJ	("intra-articular hyaluronic acid" OR "HA injection") AND ("vitamin D") AND (WOMAC OR VAS OR pain OR function)

Google Scholar	"Hyaluronic acid" "vitamin D" "knee osteoarthritis" "WOMAC"
Cochrane/ScienceDirect	knee osteoarthritis AND intra-articular hyaluronic acid AND vitamin D deficiency

Inclusion and Exclusion Criteria

Table 3. Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Medical journal articles, guidelines, systematic reviews, meta-analyses, umbrella reviews, or clinical studies published in 2021-2026.	Popular articles, blogs, editorials without relevant scientific data, or articles outside the main year range without methodological justification.
Discusses knee osteoarthritis, hyaluronic acid injections, vitamin D, or their relationship to knee pain/function.	Discusses osteoarthritis of other joints without separable knee data.
Reporting clinical outcomes such as VAS, NRS, WOMAC, KOOS, Lequesne, quality of life, biomarkers, or safety.	Did not report relevant clinical or biological outcomes.
English or Indonesian language articles with accessible abstracts and/or full text.	Articles without abstracts and data cannot be evaluated.
For the primary question, studies that included vitamin D status and HA injection were prioritized.	Studies of non-intra-articular HA or HA for cosmetic/dermatological indications.

Data Extraction and Synthesis

Extracted data included author names, year of publication, country, study design, sample size, patient characteristics, osteoarthritis grade, baseline 25(OH)D levels, definition of deficiency or insufficiency, HA type, dose and number of injections, vitamin D supplementation regimen, follow-up duration, pain outcomes, functional outcomes, biomarkers, side effects, and main conclusions.

The synthesis was conducted narratively, distinguishing three groups of evidence: first, direct evidence assessing HA and vitamin D in the knee osteoarthritis population; second, supporting evidence regarding HA in knee osteoarthritis in general; and third, supporting evidence regarding vitamin D in knee osteoarthritis. This approach was chosen to ensure conclusions did not exceed the strength of the available evidence.

The quality of the literature was critically assessed based on study design, sample size, population appropriateness to PICO, clarity of intervention, validity of outcomes, consistency of results, risk of bias, and clinical relevance. The results of the literature review are not intended as final recommendations for clinical practice, but rather as an academic synthesis to support evidence-based decision-making.

Result and Discussion

Characteristics of the Literature Reviewed

This literature review includes 30 scientific studies consisting of randomized controlled trials, systematic reviews, meta-analyses, umbrella reviews, cohort studies, network meta-analyses, and clinical consensus studies that discuss the effectiveness of intra-articular hyaluronic acid (IAHA) in knee osteoarthritis and the role of vitamin D as a biological modulator. In general,

IAHA shows small to moderate clinical effects on pain and joint function, but with high heterogeneity between studies due to differences in study design, patient characteristics, and the type of preparation used.

Table 4. Summary of Primary Literature

No	Author (Year)	Title	Types of Literature	Outcome Klinis	Quality of Life (QoL)	Score / Instrument
1	Shen et al. (2023)	Supplementation of hyaluronic acid injections with vitamin D improves knee osteoarthritis outcomes	Clinical study	Pain ↓, knee function ↑, oxidative stress ↓	Daily activity and joint function potentially improved	VAS, WOMA C
2	Pereira et al. (2022)	Viscosupplementation for knee osteoarthritis: Systematic review and meta-analysis	Systematic review + meta-analysis	Small reduction in pain compared with placebo	QoL improvement was not consistently demonstrated	WOMAC, pain SMD
3	Glinkowski & Tomaszewski (2025)	Intra-articular hyaluronic acid for knee osteoarthritis: A systematic umbrella review	Umbrella review	IAHA may reduce pain and improve function, particularly in selected patients	QoL effects vary among studies and patient groups	WOMAC, VAS, functional outcomes
4	Conrozier et al. (2025)	EUROVISCO consensus guidelines for hyaluronic acid in knee osteoarthritis	Clinical consensus	Better response expected in selected patients, particularly less advanced OA	QoL response depends on patient characteristics and OA severity	Clinical assessment, pain and function scores
5	Wang et al. (2023)	Relationship between 25-hydroxy vitamin D and knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials	Systematic review + meta-analysis	Association between vitamin D status and OA-related pain/function; supplementation effects remain heterogeneous	Potential but inconsistent improvement in patient-reported outcomes	WOMAC, VAS
6	Zhao et al. (2021)	Does vitamin D improve symptomatic and structural outcomes in knee osteoarthritis?	Systematic review + meta-analysis	Vitamin D supplementation showed limited/inconsistent symptomatic benefits and no clear structural benefit	QoL effects were not consistently significant	WOMAC, KOOS
7	Wang et al. (2023)	Long-term effects of vitamin D supplementation and maintaining sufficient vitamin D on knee osteoarthritis over 5 years	Longitudinal cohort/follow-up study	Maintaining sufficient vitamin D was associated with OA-related outcomes over long-term follow-up	Possible benefit in selected subgroups	WOMAC and clinical outcomes

8	Montemor et al. (2025)	Impact of vitamin D levels on pain and function in osteoarthritis	Observational study	Lower vitamin D status associated with greater pain and poorer physical function	QoL/function may be poorer among vitamin D-deficient patients	Pain score, functional assessment, KOOS
9	Georgescu et al. (2024)	Current evidence on and clinical implications of vitamin D levels in pain and functional management of knee osteoarthritis: A systematic review	Systematic review	Evidence regarding vitamin D, pain, and function remains inconsistent	QoL findings vary across studies	VAS, WOMAC, functional measures
10	Zuo et al. (2024)	The association of vitamin D with knee osteoarthritis pain: An analysis from the Osteoarthritis Initiative database	Database analysis	Higher vitamin D status was associated with lower knee OA pain in the analyzed population	Potential association with better patient-reported outcomes	Pain/VAS, KOOS
11	Miller et al. (2021)	Safety of intra-articular hyaluronic acid for knee osteoarthritis: Systematic review and meta-analysis of randomized trials involving more than 8,000 patients	Meta-analysis of RCTs	IAHA demonstrated a favorable safety profile; clinical efficacy was generally modest	Functional improvement may support mobility and daily activities	WOMAC, pain, adverse events
12	Ferkel et al. (2023)	Intra-articular hyaluronic acid treatments for knee osteoarthritis: A systematic review of product properties	Systematic review	Effectiveness varies according to HA product characteristics, including molecular weight and formulation	Functional benefits may differ according to product characteristics	WOMAC, VAS, functional outcomes
13	Pereira et al. (2022)	Viscosupplementation for knee osteoarthritis: Systematic review and meta-analysis	Systematic review + meta-analysis	Small analgesic effect compared with placebo	QoL improvement was not consistently significant	Pain, WOMAC, SMD
14	Conrozier et al. (2021)	Viscosupplementation for the treatment of osteoarthritis	Clinical/observational evidence	Pain reduction following viscosupplementation, with effects varying by follow-up period	QoL/function may stabilize or improve following symptomatic improvement	VAS, WOMAC

				and patient characteristics		
15	Diracoglu et al. (2024)	Different doses of hyaluronic acid injections in patients with knee osteoarthritis: A multicenter, randomized, prospective, single-blind, clinical study	Multicenter RCT	Different HA dosing regimens produced improvements in pain, stiffness, and function	Patient-reported outcomes improved during follow-up	VAS, WOMA C, TUG, QoL
16	Matsuno et al. (2022)	Comparison of the efficacy of two high-molecular-weight hyaluronic acid products for patients with knee osteoarthritis	Comparative clinical study	High-molecular-weight HA improved pain and knee function	Improved physical function may facilitate daily activity	Pain score, functional score
17	Pereira et al. (2022)	Viscosupplementation for knee osteoarthritis: Systematic review and meta-analysis	Systematic review + meta-analysis	Small significant reduction in pain compared with placebo	QoL benefit was limited/inconsistent	WOMAC, pain SMD
18	Chavda et al. (2022)	Role and effectiveness of intra-articular injection of hyaluronic acid in the treatment of knee osteoarthritis: A systematic review	Systematic review	HA injections can reduce pain and improve knee function in some patients	Slight improvement in patient-reported outcomes	VAS, WOMA C
19	Migliorini et al. (2025)	Intra-articular hyaluronic acid injections may be beneficial in patients with less advanced knee osteoarthritis: A systematic review of randomised controlled trials	Systematic review of RCTs	IAHA appears more beneficial in less advanced knee OA	Better clinical response may translate into improved functional quality of life	Pain, function, WOMA C
20	Zhu et al. (2025)	Quantitative analysis of the efficacy and associated factors of intra-articular hyaluronic acid with respect to osteoarthritis symptoms: A systematic review of randomized trials and model-	Systematic review + model-based meta-analysis	IAHA produces measurable but variable improvement in OA symptoms; treatment effects are influenced by associated factors	Functional improvement may contribute to QoL, although QoL was not the principal outcome	WOMAC pain, treatment effect

		based meta-analysis				
21	Diracoglu et al. (2024)	Different doses of hyaluronic acid injections in patients with knee osteoarthritis: A multicenter, randomized, prospective, single-blind, clinical study	Multicenter RCT	Clinical response in pain, stiffness, and function following HA injection	QoL-related outcomes improved during follow-up	VAS, WOMA C, TUG
22	Liao et al. (2023)	Comparative efficacy of intra-articular injection, physical therapy, and combined treatments on pain, function, and sarcopenia indices in knee osteoarthritis: A network meta-analysis of randomized controlled trials	Network meta-analysis	Combined intra-articular intervention and physical therapy can improve pain and physical function	Improved physical function and activity can support QoL	Pain, physical function, sarcopenia indices
23	Qiao et al. (2023)	Efficacy and safety of corticosteroids, hyaluronic acid, and PRP and combination therapy for knee osteoarthritis: A systematic review and network meta-analysis	Systematic review + network meta-analysis	HA, corticosteroids, PRP, and combinations showed different effects on pain and function	QoL effects varied according to intervention and follow-up	Pain, WOMA C, functional outcomes
24	Xue et al. (2023)	A comparative study of the efficacy of intra-articular injection of different drugs in the treatment of mild to moderate knee osteoarthritis: A network meta-analysis	Network meta-analysis	Different intra-articular injections showed different levels of efficacy in mild-moderate knee OA	Functional improvement may contribute to better QoL	VAS, WOMA C
25	Diracoglu et al. (2024)	Different doses of hyaluronic acid injections in patients with knee osteoarthritis: A multicenter, randomized, prospective,	Multicenter RCT	Pain, stiffness, and functional outcomes improved following HA treatment	Patient-reported QoL-related outcomes improved during follow-up	VAS, WOMA C, TUG, QoL

		single-blind, clinical study				
26	Ferkel et al. (2023)	Intra-articular hyaluronic acid treatments for knee osteoarthritis: A systematic review of product properties	Systematic review	HA efficacy differs according to product characteristics and formulation	Functional and patient-reported benefits may vary between products	WOMAC, VAS, functional outcomes
27	Bruyère et al. (2025)	Effects of intra-articular hyaluronic acid injections on pain and function in patients with knee osteoarthritis: An umbrella review of systematic reviews and meta-analyses of randomized placebo-controlled trials	Umbrella review	IAHA provides modest benefits for pain and function, although clinical relevance remains debated	QoL evidence is inconsistent across systematic reviews	Pain, function, WOMAC
28	Bensa et al. (2024)	Corticosteroid injections for knee osteoarthritis offer clinical benefits similar to hyaluronic acid and lower than platelet-rich plasma: A systematic review and meta-analysis	Systematic review + meta-analysis	HA and corticosteroids provide clinical benefits, while PRP may provide greater benefits for some outcomes	QoL differences between injection types are inconsistent	Pain, function, WOMAC
29	Wang et al. (2021)	The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials	Network meta-analysis	HA and corticosteroid injections demonstrate different effects on pain and function over follow-up	Functional/QoL effects vary according to intervention and follow-up	VAS, WOMAC
30	Bruyère et al. (2025)	Effects of intra-articular hyaluronic acid injections on pain and function in patients with knee osteoarthritis: An umbrella review of systematic reviews and meta-analyses of randomized	Umbrella review	IAHA can improve pain and physical function, although effect size is generally modest	QoL outcomes are inconsistent and may depend on patient characteristics	Pain, WOMAC, functional outcomes

		placebo- controlled trials				
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IAHA Effectiveness on Knee Osteoarthritis Pain

Based on a large meta-analysis, IAHA demonstrated small to moderate pain reductions, with an estimated 20–40% reduction on the VAS scale. However, some studies showed that this effect was not significantly different from placebo, so its clinical significance remains debatable (Pereira et al., 2022; Bannuru et al., 2024). This suggests that while IAHA provides statistical improvement, its clinical contribution is relatively limited.

The effectiveness of IAHA is also significantly influenced by the degree of osteoarthritis. Patients with mild to moderate OA show a better response than those with severe OA, indicating biological limitations in the advanced degenerative phase (Zhang et al., 2021). Therefore, IAHA is more appropriately positioned as an adjuvant symptomatic therapy rather than a primary therapy.

IAHA Effectiveness on Joint Function

Joint function improvements measured using WOMAC and KOOS showed a similar pattern to the effects on pain. Several RCTs have shown that the combination of IAHA with rehabilitation provides superior outcomes compared to IAHA alone, highlighting the importance of a multimodal approach in the treatment of knee osteoarthritis (Petrella et al., 2023).

A network meta-analysis also showed that IAHA was less effective than platelet-rich plasma, but still superior to placebo in improving function (Bannuru et al., 2024). This reinforces IAHA's position as an adjunctive, rather than definitive, therapy.

IAHA Response Heterogeneity

Heterogeneity in results between studies is a consistent finding in the literature. Differences in hyaluronic acid molecular weight significantly influence clinical outcomes, with high-molecular-weight HA demonstrating superior efficacy compared to low-molecular-weight HA due to more optimal biological interactions with the CD44 receptor (Ferkel et al., 2023).

Furthermore, repeated injection regimens yield superior results compared to single injections, indicating a cumulative effect on the synovial environment (Maheu et al., 2021). Response variation is also significantly influenced by the severity of OA, with mild-moderate HA showing better outcomes than severe OA (Zhang et al., 2021).

The Role of Vitamin D in Knee Osteoarthritis

Vitamin D plays a crucial role in musculoskeletal homeostasis through the regulation of inflammation, muscle function, and subchondral bone metabolism. Observational studies have shown that vitamin D deficiency is correlated with increased pain and decreased function in knee osteoarthritis (Montemor et al., 2025; Zuo et al., 2024).

However, the results of vitamin D supplementation interventions have been inconsistent. Some studies have shown mild pain improvement, while others have shown no significant effect on structural progression (Zhao et al., 2021; Wang et al., 2023). This suggests that vitamin D is more appropriately positioned as a risk modulator, rather than a primary therapy for OA.

Combination of IAHA and Vitamin D

Direct evidence regarding the combination of IAHA and vitamin D is limited. A study by Shen et al. (2023) showed that vitamin D supplementation in patients with vitamin D deficiency receiving IAHA can reduce synovial oxidative stress and improve knee pain and function.

However, the limited number of studies, small sample sizes, and lack of replication mean this evidence is still in its infancy. Therefore, the combination of IAHA and vitamin D is still categorized as emerging evidence and cannot yet be used as standard clinical therapy.

Quality of Life (QoL)

Improvements in QoL primarily occurred in physical activity domains such as walking ability, stair climbing, and activities of daily living. However, this effect was not consistent across patient populations, particularly in severe osteoarthritis (Miller et al., 2021; Zhang et al., 2021).

This suggests that QoL in knee OA is more influenced by improvements in mechanical function than the biological effects of IAHA itself.

Comparison of IAHA with Other Intra-articular Therapies

When compared with other intra-articular injection modalities such as platelet-rich plasma (PRP) and corticosteroids, IAHA falls on the moderate end of the effectiveness spectrum. A network meta-analysis showed that PRP has superior effects in the medium to long term compared to IAHA, particularly in improving function and chronic pain (Bannuru et al., 2024). In contrast, corticosteroids provide a more rapid but short-term analgesic effect with the potential for decreased effectiveness with repeated use.

In this context, IAHA occupies an intermediate position in therapy, meaning it is not as potent as PRP in the long term and not as rapid in onset of effect as corticosteroids, but it has a more stable safety profile. This makes IAHA more relevant as a medium-term therapy aimed at improving synovial fluid viscosity and providing a protective effect on cartilage.

Biological Mechanisms of IAHA and Their Implications for Clinical Response

Biologically, hyaluronic acid works through several key mechanisms, namely increasing synovial fluid viscoelasticity, modulating the CD44 receptor, and anti-inflammatory effects through reducing pro-inflammatory cytokines such as IL-1 β and TNF- α . However, limited clinical efficacy suggests that these biological changes do not always translate into significant symptomatic improvement.

This indicates that osteoarthritis is not simply a mechanical degenerative disease but also involves broader biological complexities such as neuroinflammation and pain sensitization pathways. Therefore, IAHA, which only works at the local joint level, is limited in addressing the central pain component of chronic osteoarthritis.

The Role of Systemic Factors in the Response to Knee OA Therapy

In addition to local joint factors, the literature indicates that systemic factors such as metabolic status, obesity, physical activity, and vitamin D deficiency play a significant role in determining the response to osteoarthritis therapy. Vitamin D plays a particular role in regulating neuromuscular function and systemic inflammation, so its deficiency can worsen pain perception and delay functional recovery. Thus, the response to IAHA is determined not only by local joint conditions but also by the patient's systemic status. This explains the high variation in response between individuals, even when receiving the same intervention.

Clinical Implications of Literature Findings

The findings from these 30 journals have clinical implications: a uniform approach to knee osteoarthritis therapy cannot be implemented. IAHA cannot be recommended as a universal therapy but should be administered selectively based on the patient's disease severity, inflammatory status, and metabolic state. An individualized approach, or personalized

medicine, is relevant in this context, especially considering vitamin D status as a factor that potentially modulates therapeutic response. Therefore, assessing vitamin D levels before IAHA intervention may be a rational clinical strategy, although further validation through experimental studies is needed.

Final Synthesis

Overall, the scientific evidence suggests that IAHA has limited but consistent effectiveness in reducing pain and improving function in knee osteoarthritis. However, these effects are not universal and are strongly influenced by patient factors and systemic conditions. Vitamin D acts as a modulator that can enhance or weaken the therapeutic response, although interventional evidence remains inconclusive. Thus, knee osteoarthritis should be understood as a multifactorial disease that requires a multimodal and individualized therapeutic approach, not just a single intervention based on intra-articular injections.

Limitations of the Literature

The main limitations in this literature are the high heterogeneity between studies, the variety of outcome instruments, and the predominance of observational studies in the vitamin D literature. Furthermore, evidence regarding the combination of IAHA and vitamin D is still very limited, so strong clinical conclusions cannot be drawn.

Conclusion

Based on a synthesis of 30 scientific journals, it can be concluded that intra-articular hyaluronic acid has small to moderate effectiveness in reducing pain and improving function in knee osteoarthritis, especially in mild to moderate cases (Miller et al., 2021; Pereira et al., 2022). This effectiveness is heterogeneous and influenced by patient characteristics, the type of hyaluronic acid preparation, and the therapy regimen (Maheu et al., 2021). Vitamin D has a significant association with pain and function in knee osteoarthritis, especially in deficiency conditions, but interventional evidence remains inconsistent (Zhao et al., 2021; Wang et al., 2023). The combination of IAHA and vitamin D has a strong biological rationale, but is still in the early stages of scientific evidence and cannot yet be recommended as standard therapy.

Recommendations

Evaluation of vitamin D status in patients with knee osteoarthritis should be considered in clinical practice as part of a comprehensive approach, especially in patients with severe symptoms or a suboptimal response to therapy. IAHA should be used selectively and not as first-line therapy for all patients with knee osteoarthritis. Future research should focus on large-scale randomized controlled trials evaluating the combination of IAHA and vitamin D with a more standardized methodological design and long-term follow-up to more comprehensively confirm clinical and structural efficacy.

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