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ORIGINAL RESEARCH

10 years of real-world data: long-term efficacy and safety of HyalOne® for hip osteoarthritis

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Abstract

Background: Hip osteoarthritis (OA) is a leading cause of disability in older adults, yet long-term, non-surgical treatment options remain limited. Viscosupplementation with intra-articular hyaluronic acid has shown promise, but evidence for its sustained efficacy in hip OA is scarce. This study evaluates the 10-year efficacy and safety of repeated ultrasound (US)-guided injections of HyalOne®/Hyalubrix® 60 in patients with symptomatic hip OA.

Methods: A retrospective, observational, open-label study was conducted on 681 patients with symptomatic hip OA treated with HyalOne® between 2010 and 2013, with follow-up through 2023. Patients received one US-guided intra-articular injection every 6 months, with additional injections as needed. Pain and functional outcomes were assessed using the Visual Analogue Scale and the Lequesne Index. Non-steroidal anti-inflammatory drug (NSAID) consumption and adverse events were also monitored.

Results: Overall, 481 patients completed the 10-year follow-up. Pain reduction was observed across all age and body mass index groups, with the highest improvement in patients under 40 years old (−54.3%). Functional status improved significantly, with the greatest reduction in Lequesne Index scores observed in patients over 80 years old (−32.5%). NSAID use decreased by 84% in younger patients and by 62–71% in older patients or those with obesity. No major systemic adverse events were reported, and transient local reactions occurred in 4% of patients.

Conclusions: This study provides the first real-world evidence of the sustained efficacy and safety of a 10-year US-guided HyalOne® injection regimen in managing hip OA, highlighting significant improvements in pain, function and NSAID reduction across diverse patient populations.

Keywords: hip, hyaluronic acid, osteoarthritis, viscosupplementation.

Citation

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Introduction

Osteoarthritis (OA) is the leading cause of joint pain in adults, particularly in older individuals, contributing to disability and social isolation, especially when the hip or knee is affected. The prevalence of hip OA reaches 17% in white males and 9% in white females over the age of 60 years.[1] Treatment focuses on preserving joint mobility and alleviating pain.[2] Whilst non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics provide symptomatic relief, long-term use can lead to adverse effects, particularly in

older patients with comorbidities. Since the late 1990s, viscosupplementation (VS), involving intra-articular (IA) hyaluronic acid (HA) injections, has emerged as a promising alternative.[3] However, most evidence focuses on knee OA, leaving hip OA underexplored, and discrepancies persist between guidelines and clinical practice.[4,5]

HyalOne® is a sterile, high-molecular-weight (1500–2000 kDa) HA solution produced by bacterial fermentation that has been marketed globally since 2009 (HYAP15 data on file).[6] It is indicated for pain relief and functional improvement in hip and knee OA, particularly in cases of analgesic or NSAID failure.[7,8] Although IA HA use for hip OA has expanded,[9] long-term data and systemic evidence on its efficacy and safety remain limited.[10–13]

A randomized controlled trial reported significant reductions in Lequesne Index scores at 3 and 6 months compared with anaesthetics.[14] An observational study of 120 patients who received HyalOne® injections every 6 months over an 18-month period found that 80% experienced symptom reductions by 12 months.[15] Another study of 176 patients revealed that 90% avoided total hip replacement (THR) at 24 months, with 82% maintaining this outcome at 48 months.[16] A long-term follow-up study published in 2017 by Migliore et al. assessed the efficacy of ultrasound (US)-guided HyalOne® (60 mg/4 mL) injections, administered at least twice a year for up to 7 years, involving 1022 patients with hip OA. Regardless of age or body mass index (BMI), all patients experienced significant improvements in assessment scores 6 months post-treatment, with repeated HA injections maintaining efficacy for up to 7 years. No systemic or severe local side-effects were reported during the study period.[17]

This real-world study aims to evaluate the efficacy of repeated courses of US-guided HyalOne® injections in a retrospective cohort of patients with symptomatic intermediate-stage hip OA over a 10-year period.

Patients and methods

Study design

This retrospective, observational, open-label, post-marketing study included patients with symptomatic hip OA who were treated with IA injections of HyalOne®. Data were sourced from patient records at Saint Peter Hospital in Rome and analysed using descriptive and analytical statistics to evaluate the long-term efficacy and safety of the treatment.

Patient selection

The study analysed the records of outpatients with symptomatic hip OA who were treated with HyalOne®, enrolled between 1 January 2010, and 31 December 2013, and followed up until 31 December 2023, for a maximum follow-up duration of 10 years. All patients included in the study were monitored through clinical visits performed approximately every 6 months. Data from baseline and follow-up visits were recorded in the ANTIAGE Registry.[18]

Inclusion criteria required patients to be at least 18 years old with a diagnosis of symptomatic hip OA, established according to the American College of Rheumatology criteria,[19] persisting for at least 1 year. Exclusion criteria were the use of oral anticoagulant therapy or the presence of significant comorbidities, such as rheumatological diseases, lower back pain or femoral head osteonecrosis, which could potentially confound the results.

In January 2024, a team of investigators extracted data from the registry, applying the predefined inclusion and exclusion criteria. Baseline information included demographic data, clinical history and radiographic assessments. Hip radiographs were assessed using the Kellgren and Lawrence grading scale,[20] based on non-weight-bearing X-rays obtained within 6 months prior to the initial injection. Pain levels were assessed using a 100 mm Visual Analogue Scale (VAS), whilst functional status was measured using the Lequesne Index.[21]

Patients received IA injections of HyalOne® at a dose of 60 mg/4 mL into the affected hip every 6 months, ranging from 4 to 10 months depending on symptoms and patient availability. If clinically indicated, additional injections were administered, with a maximum of one injection every 3 months within a single year. The 6-month injection schedule was maintained even in patients reporting symptomatic improvement as part of a strategy to preserve clinical benefits and mitigate disease progression. All injections were performed under US guidance to ensure precise delivery into the joint space.[15]

Clinical evaluations were conducted every 3 months throughout the 10-year follow-up, assessing pain on a 100 mm VAS and functional status using the Lequesne Index, in accordance with routine clinical and therapeutic practice in the Rheumatology Service (Rheumatology Unit and Research Center, S. Pietro FBF Hospital, Rome, Italy). These data were systematically collected by trained nursing staff during in-person visits conducted prior to each intra-articular infiltration. Patients did not receive diaries; instead, they provided VAS ratings and information on the number of days per month they used anti-inflammatory medications through structured interviews.

To exclude relevant structural deterioration in patients who showed poor response to treatment or reported worsening symptoms, patients underwent hip radiographs approximately every 2–3 years at different external

Table 1. Number of dropouts.

Dropouts	*n*
Total number of enrolled patients	681
Total number of dropouts	200
• Surgery	82
• Unfound	90
• Died	28
Total population in the study	481

radiology centres without centralized acquisition protocols or image reading. As such, Kellgren-Lawrence (K-L) grading or other radiographic classifications were not consistently applied or systematically recorded.

Dropouts included patients who were lost to follow-up because of non-presentation to control visits or injection sessions, those referred to other clinical facilities, patients who died, and those who underwent THR. A notable proportion of participants were aged over 80 years old at the start of the study, contributing to the dropout rate over the extended follow-up period.

Statistical analysis

Descriptive statistics were used to summarize the patient population and subgroups included in this study, where appropriate. For continuous variables, summary measures included the mean, standard deviation, range and sample size, whereas for discrete variables, they included counts and proportions. Changes in the Lequesne Index, pain VAS and NSAID intake were compared with baseline at each study point using the Wilcoxon test for paired data to determine statistically significant differences. The alpha value was adjusted to account for multiple comparisons, given the number of analyses performed on each variable. The odds ratio and the corresponding confidence interval (CI) were calculated at p=0.05 and were analysed across patient groups. The patient population was categorized at baseline by age into the following groups: patients under 40 years, patients aged 41–59 years, patients aged 60–79 years and patients aged 80 years and older. Another classification was based on BMI, with patients categorized as having normal weight, overweight or obesity.

Ethics approval

All participants provided informed written consent prior to enrolment in the study. All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments. This study was approved by the Ethics Committee. All patients released informed consent to participate.

All the data were obtained from the ANTIAGE Registry and were approved by the Ethics Committee of Azienda Ospedaliera San Camillo Forlanini, Rome. The following variables were analysed: age, categorized at baseline;

Table 2. Baseline characteristics of the study population up to 10 years.

Characteristics	*n*=481
Sex	
• Males	231 (48%)
• Females	250 (52%)
Age (years), mean ± SD	63 ± 11.9
BMI, mean ± SD	26.6 ± 2.9
Weight (kg), mean ± SD	75.1 ± 13.9
Height (cm), mean ± SD	167.8 ± 9.3
Smoking habit	65 (13.51%)
Lequesne Index mean	8.93 ± 4.7
Pain VAS mean	7.01 ± 2.26
NSAID intake (days/month), mean ± SD	8.24 ± 8.3
Concomitant knee OA	388 (38%)
Diabetes	24 (4.9%)
Classes (years)	
• Under 40	14 (3%)
• 40–59	168 (35%)
• 60–79	256 (53%)
• Over 80	43 (9%)
Affected hip	
• Right	278 (57.8%)
• Left	203 (42.2%)
Kellgren and Lawrence grading scale	
• Grade I	49 (10.1%)
• Grade II	252 (52.4%)
• Grade III	137 (28.6%)
• Grade IV	43 (9%)
BMI categorization	
• Normal weight	176 (37%)
• Overweight	201 (42%)
• Obesity	104 (21%)

Data are presented as *n* (%) or mean ± SD.

Lequesne Index, classified as low (index 4), moderate (index 5–7) or high (index 8); US pattern, where baseline hip US was used to classify patients into regular *versus* non-regular profiles. Radiographic assessments were based on the Kellgren and Lawrence grading scale. Responder status was determined for both the Lequesne Index and pain VAS. A patient was considered a responder if their Lequesne Index decreased by at least 30% compared with baseline for at least two consecutive study points. Similarly, a patient was classified as a responder for pain VAS if they exhibited at least a 30% reduction from baseline for at least two consecutive study points. Time to response was defined as the duration between the baseline and the first study point at which a responder achieved a 30% reduction in the respective measure.

Results

Patient population

A total of 681 patients were enrolled at the start of the study. Over the 10-year follow-up period, 200 (35.5%) patients were lost to follow-up, resulting in 481 patients completing the study, with a mean age of 63 (±11.9) years. Reasons for dropout are reported in Table 1.

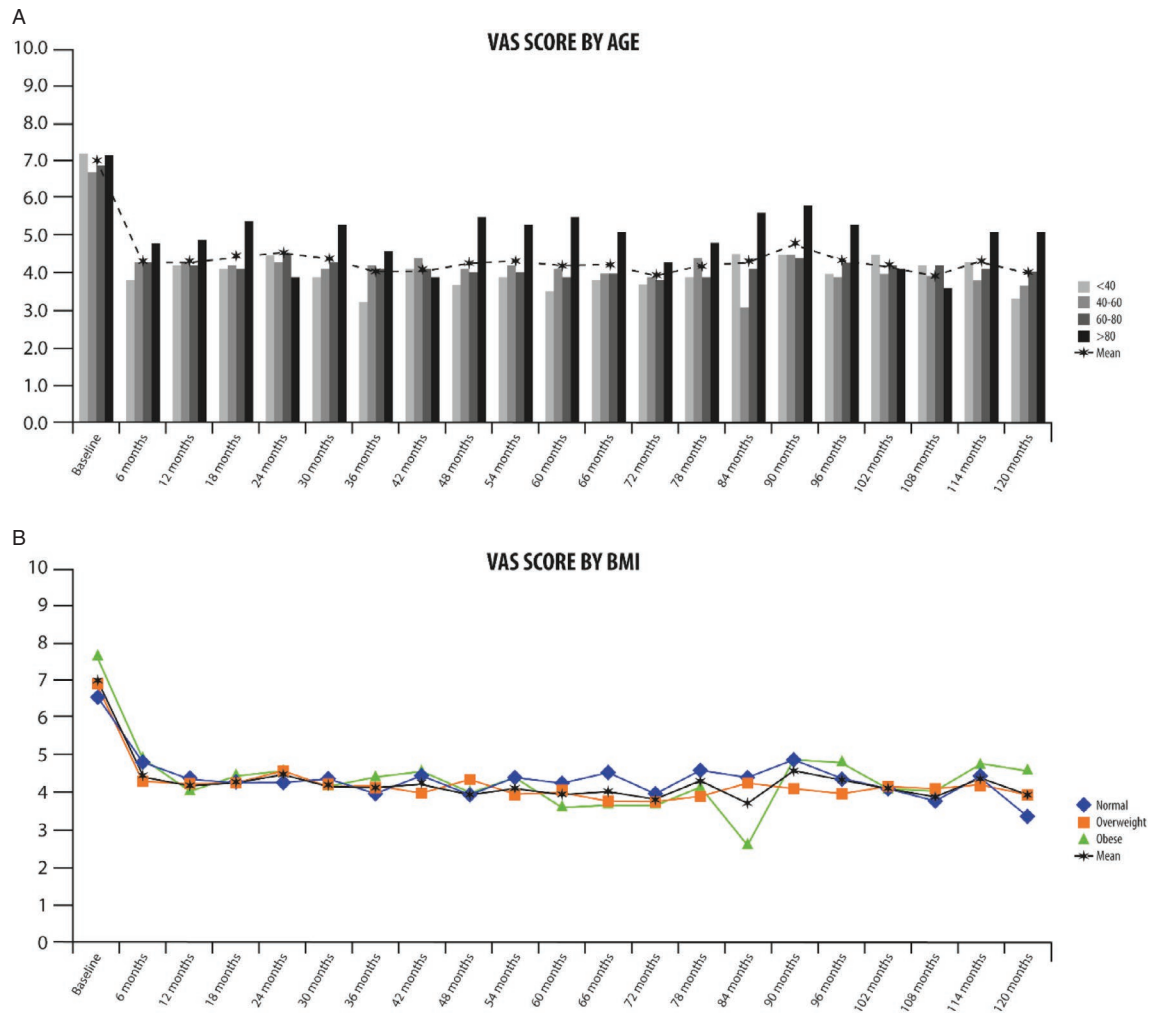
The demographic characteristics of the study population are summarized in Table 2. The study population consisted of 231 (48%) men and 250 (52%) women, with a mean BMI of 26.6 (±2.9). By BMI classification, 176 patients were categorized as having normal weight (BMI 18–25), 201 as having overweight (BMI 25–30) and 104 as having obesity (BMI 30–35). Concomitant knee OA was present in 388 (38%) patients, and 24 (4.9%) patients had diabetes.

Pain reduction (VAS score)

Results by age

A statistically significant reduction was observed at all-time points compared with baseline values (Figure 1A). At baseline, patients under 40 years old and those over 80 years old reported the highest pain scores (7.2). By 6 months, the under-40 group exhibited the most substantial reduction (−47%), whilst patients over 80 showed

Figure 1. VAS scores over 120 months, categorized by (A) age and (B) BMI.



a more modest decrease (−20%). At the final 120-month evaluation, pain reduction remained greatest in patients under 40 years (−54.3%), followed by those aged 40–59 years (−45.3%) and 60–79 years (−41.3%). Patients aged 80 and older demonstrated a smaller but significant reduction of 29% (Figure 2).

Results by BMI

When categorized by BMI, all groups showed a statistically significant reduction at 6 months, which persisted through 120 months (Figure 1B). Baseline VAS scores ranged from 6.5 (normal weight patients) to 7.7 (patients with obesity). Pain reduction at 6 months was consistent across all BMI categories from 4.3 to 4.9, with sustained improvements at 120 months (VAS range: 3.4–4.7) (Figure 3).

Functional improvement (Lequesne Index)

Results by age

All groups showed a statistically significant reduction at all-time points compared with baseline values (Figure 4A). Baseline Lequesne Index scores increased progressively with age, with patients aged 80 and older reporting the highest values (12.9) and those under 40 years the lowest (7.3). Over 6 months, the greatest percentage reduction was observed in the under-40 group (33%). By the final 120-month assessment, the under-40 group maintained the highest rate of improvement (−34.3%), followed by patients aged 80 and older (−32.5%), whilst those aged 40–59 years and 60–79 years showed reductions of −27.8% and −22.3%, respectively (Figure 5).

Results by BMI

When categorized by BMI, all groups showed a statistically significant reduction at 6 months, which persisted through 120 months (Figure 4B). Patients with normal weight and those with overweight had similar baseline values (7.3 and 8.3, respectively) and showed a similar decrease at 6 months (5.9 (−19%) and 6.7 (−19%), respectively). Patients with obesity had the highest baseline Lequesne Index scores (11.2), which decreased to 7.4, with a

Figure 2. VAS scores at baseline, 6 and 120 months by age.

Category	Baseline	6 Months	120 Months	% Reduction at 6 Months	% Reduction at 120 Months
Age (years)					
Under 40	7.2 ± 1.2 (CI 95%:6.9–7.5)	3.8 ± 1.1 (CI 95%: 3.5–4.1)	3.3 ± 1.1 (CI 95%: 3.0–3.6)	-47%	-54.3%
40-59	6.9 ± 1.2 (CI 95%: 6.7–7.1)	4.4 ± 1.1 (CI 95%: 4.2–4.6)	3.8 ± 1.1 (CI 95%: 3.6–4.0)	-35.9%	-45.3%
60-79	6.8 ± 1.2 (CI 95%: 6.6–7.0)	4.3 ± 1.1 (CI 95%: 4.1–4.5)	4.0 ± 1.1 (CI 95%: 3.8–4.2)	-37%	-41.3%
Over 80	7.2 ± 1.2 (CI 95%: 6.9–7.5)	5.8 ± 1.1 (CI 95%: 5.6–6.0)	5.1 ± 1.1 (CI 95%: 4.9–5.3)	-20%	-29%

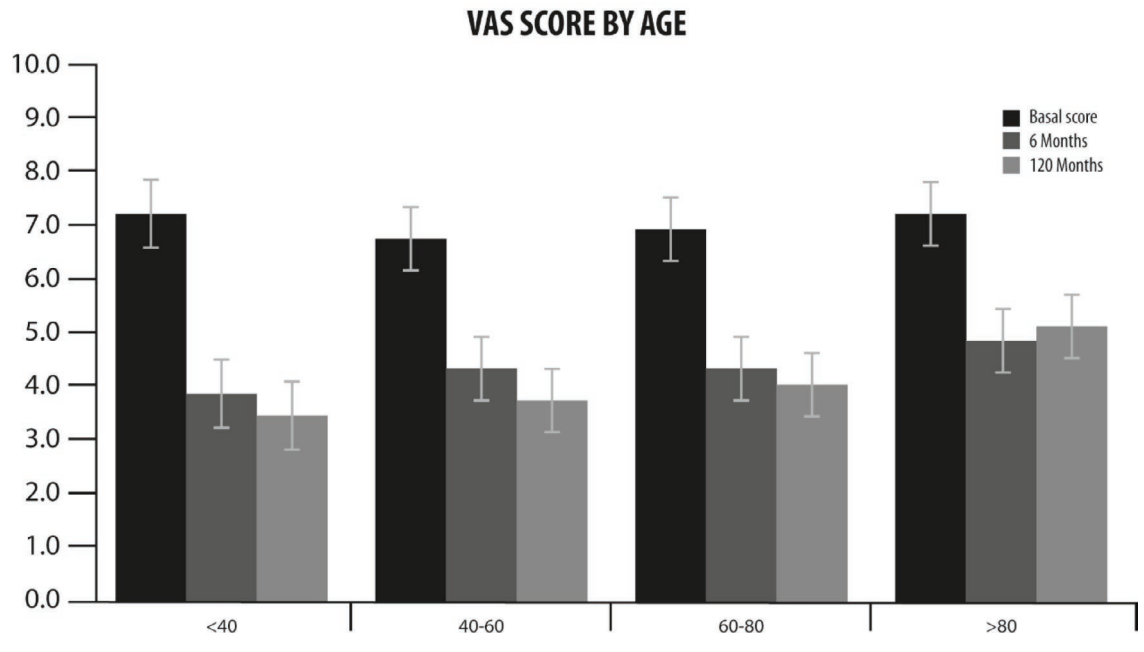
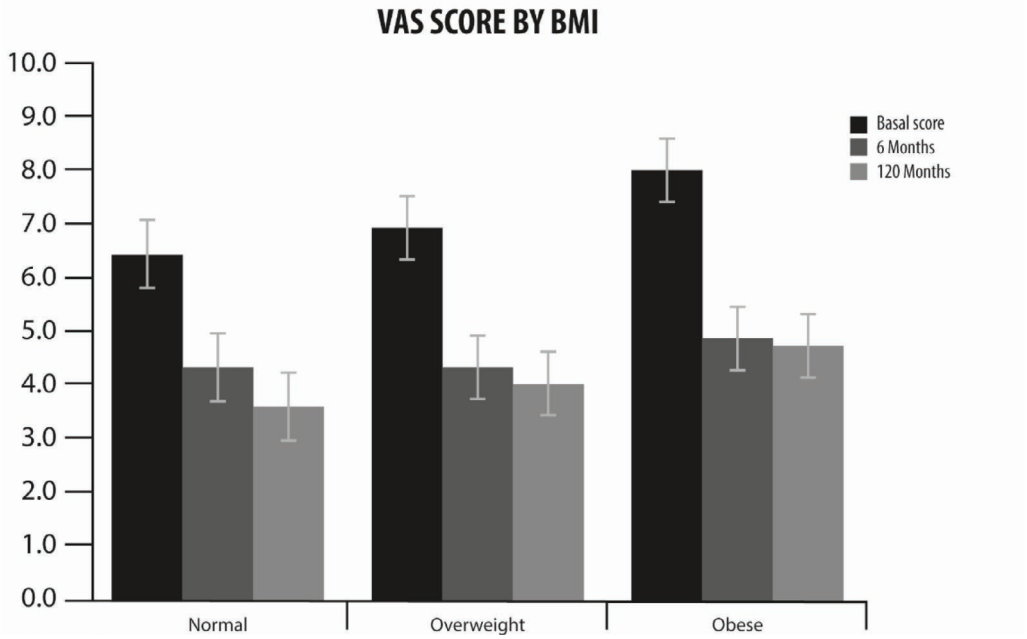


Figure 3. VAS scores at baseline, 6 and 120 months by BMI.

Category	Baseline	6 Months	120 Months	% Reduction at 6 Months	% Reduction at 120 Months
BMI					
Normal (18-25)	6.5 ± 1.2 (CI 95%: 6.3–6.7)	4.3 ± 1.1 (CI 95%: 4.1–4.5)	3.4 ± 1.1 (CI 95%: 3.2–3.6)	-33%	-47%
Overweight (25-30)	6.7 ± 1.2 (CI 95%: 6.5–6.9)	4.5 ± 1.1 (CI 95%: 4.3–4.7)	3.7 ± 1.1 (CI 95%: 3.5–3.9)	-32.8%	-45%
Obese (30-35)	7.7 ± 1.2 (CI 95%: 7.5–7.9)	4.9 ± 1.1 (CI 95%: 4.7–5.1)	4.7 ± 1.1 (CI 95%: 4.5–4.9)	-35.5%	-39.5%



33% reduction at 6 months. At the final assessment (120 months), the normal-weight group showed the lowest percentage reduction compared with baseline values (−23%), whereas patients with obesity and those who were overweight demonstrated similar improvements (−32%) (Figure 6).

Reduction in NSAID consumption

Results by age

All groups showed a statistically significant reduction at all-time points compared with baseline values (Figure 7A). At baseline, patients under 40 years reported the lowest NSAID use (5.9 days/month), whilst those aged 80 years and older had the highest consumption (9.6 days/month).

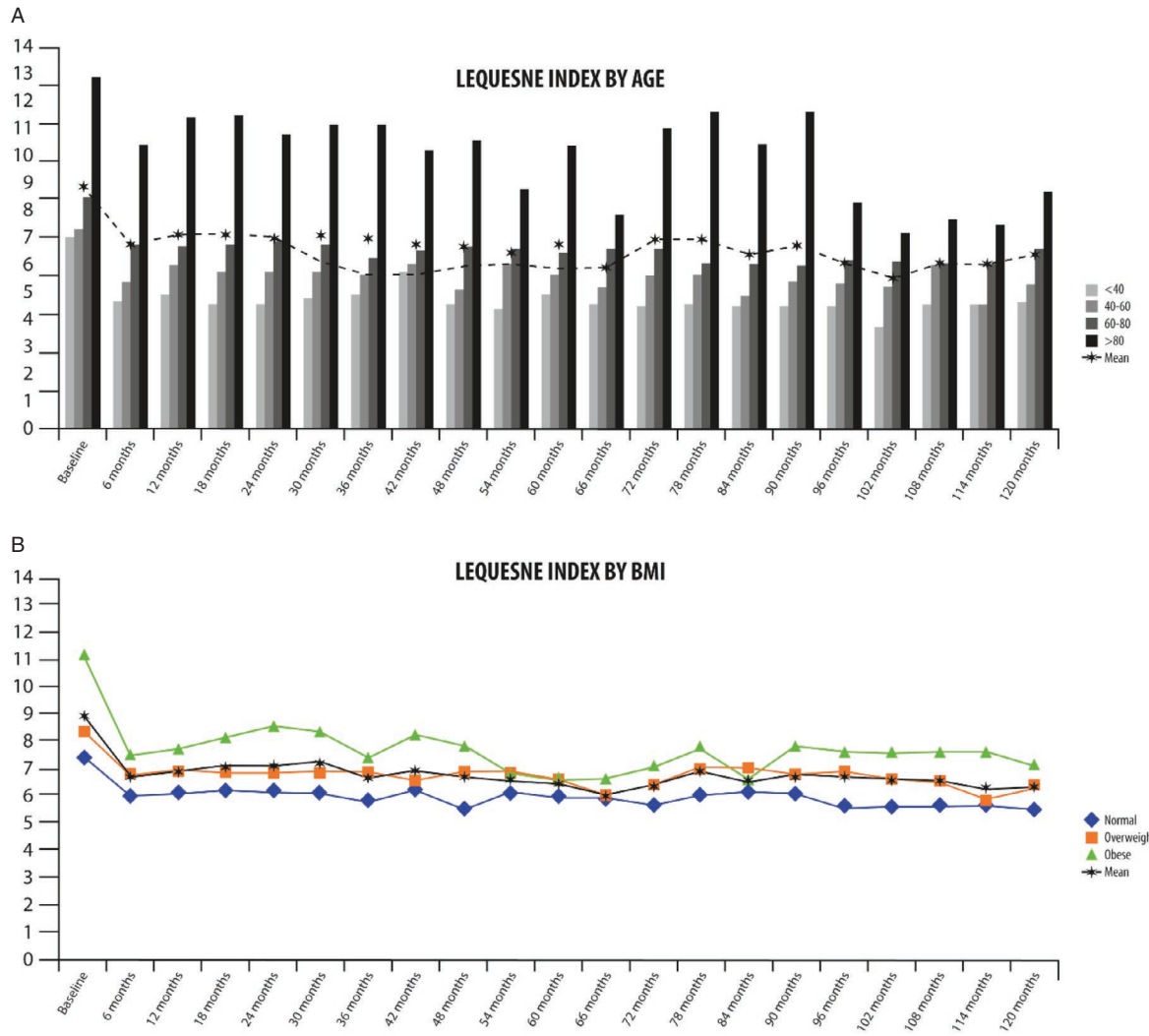
After 6 months, NSAID use dropped by 59% in the under-40 group and by 59%, 57% and 50% in patients aged 40–59 years, 60–79 years, and 80 years and older, respectively. By the final assessment, NSAID use fell to 0.9 days/month (−84%) in patients under 40 years, whilst patients aged 40–59 years, 60–79 years, and 80 years and older decreased to 2.1 days/month (−71%), 3.1 days/month (−64%) and 3.1 days/month (−68%), respectively.

Results by BMI

When categorized by BMI, all groups showed a statistically significant reduction at 6 months, which persisted through 120 months (Figure 7B). Patients with normal weight and those with overweight had similar baseline values (7.2 and 7.9 days/month, respectively) and showed a similar decrease at 6 months (3.6 days/month (−50%) and 3.5 days/month (−55%), respectively). At 120 months, the normal-weight group achieved the greatest reduction, reaching 1.4 days/month (−80%), whilst the overweight group decreased to 2.1 days/month (−73%). Patients with obesity had the highest baseline NSAID use (9.6 days/month), which decreased to 4.9 days/month (−48%) at 6 months and further declined to 3.6 days/month (−62%) at 120 months.

Detailed information about VAS scores, Lequesne Index and average NSAID intake by BMI and age is reported

Figure 4. Lequesne Index over 120 months categorized by (A) age and (B) BMI.



in the Supplementary Material (Table S1 and Table S2; available at: https://www.drugsincontext.com/wp-content/uploads/2025/07/dic.2025-3-4-Suppl.pdf).

Safety and adverse events

The safety profile of HyalOne® was favourable and consistent with previous studies.[15–17] No major systemic adverse events were observed. Mild, transient localized pain at the injection site was reported in 4% of patients, typically lasting from a few hours to several days and easily managed with minimal analgesic use. The frequency of adverse events did not increase with repeated injections, reinforcing the long-term safety of the treatment.

Discussion

This study is the first to present a decade-long analysis of the efficacy and safety of US-guided HyalOne® injections in a large cohort of patients with intermediate-to-advanced symptomatic hip OA. The data demonstrate clinical efficacy in pain reduction, decreased NSAID use and improved joint function, with a safety profile consistent with prior research.

US-guided HyalOne® injections, administered every 6 months or every 3 months when clinically indicated, effectively controlled symptoms. US guidance ensured precise HA delivery and minimized local side-effects from inadvertent extra-articular injections. These findings support the use of HyalOne® as a maintenance therapy for managing hip OA alongside other pharmacological and non-pharmacological interventions. The study provides real-world data showing sustained symptom control and NSAID reduction, irrespective of age or BMI, in a cohort representative of the typical OA population.

Patients aged 60 years and older constituted 62% of the study population, highlighting the long-term utility

Figure 5. Lequesne index at baseline, 6 and 120 months by age.

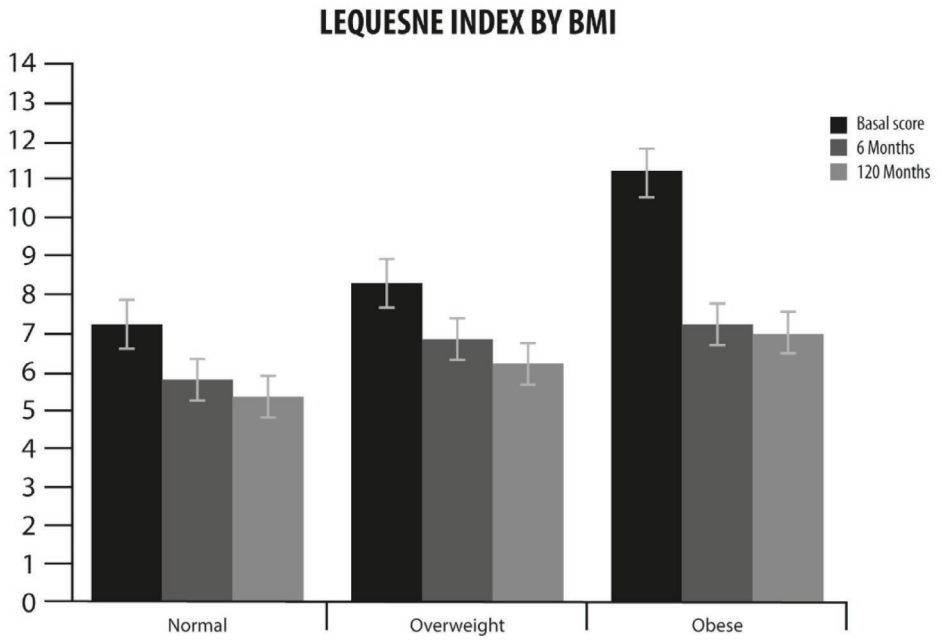
Category	Baseline	6 Months	120 Months	% Reduction at 6 Months	% Reduction at 120 Months
Age (years)					
Under 40	7.3 ± 1.5 (CI 95%: 6.9–7.7)	4.7 ± 1.4 (CI 95%: 4.3–5.1)	4.6 ± 1.4 (CI 95%: 4.2–5.0)	-33%	-34.3%
40-59	8.3 ± 1.5 (CI 95%: 8.1–8.5)	6.0 ± 1.4 (CI 95%: 5.8–6.2)	6.0 ± 1.4 (CI 95%: 5.8–6.2)	-27.7%	-27.8%
60-79	9.5 ± 1.5 (CI 95%: 9.3–9.7)	7.4 ± 1.4 (CI 95%: 7.2–7.6)	7.4 ± 1.4 (CI 95%: 7.2–7.6)	-22.1%	-22.3%
Over 80	12.9 ± 1.5 (CI 95%: 12.6–13.2)	9.0 ± 1.4 (CI 95%: 8.7–9.3)	8.7 ± 1.4 (CI 95%: 8.4–9.0)	-30.2%	-32.5%

of VS in older adults. However, differences in treatment response based on patient categorization by age and BMI can help predict the extent and rate of efficacy in specific subgroups. All patients experienced significant pain reduction over 10 years, ranging from 29% to 54%, a magnitude considered clinically meaningful. Functional improvement, assessed via the Lequesne Index, revealed that patients aged 80 years and older had the highest baseline scores. This subgroup showed significant improvement within 3 months post-injection, ultimately achieving a 32% reduction by the study's conclusion. These differences in treatment response by patient categorization may guide future studies in identifying optimal candidates for VS and predicting successful outcomes.

VS in real-world setting appears to be an effective strategy for managing pain and reducing painkiller use. Patients treated with HA experienced a significant reduction in monthly NSAID usage, starting as early as the first month of therapy and remaining reduced over time. This reduction is particularly important given the side-effects associated with prolonged NSAID use, including gastrointestinal, renal and cardiovascular complications, which are especially concerning for patients with OA who are older and have overweight. Consistent with previous literature, our findings suggest that HA injections minimize the need for NSAIDs and analgesics, thereby reducing the risk of associated complications. EUROVISCO members have further emphasized the benefits of VS for patients unable to use oral analgesics, NSAIDs or corticosteroids due to coexisting conditions, such as diabetes, hypertension, kidney failure or gastrointestinal issues or because of treatments for these conditions. From a cost perspective, reduced NSAID consumption not only lowers direct expenses but also decreases indirect costs, including those related to gastroprotective medications such as proton pump inhibitors or misoprostol and hospitalizations for gastrointestinal or cardiovascular side-effects. This study is the first to demonstrate the

Figure 6. Lequesne index at baseline, 6 and 120 months by BMI.

Category	Baseline	6 Months	120 Months	% Reduction at 6 Months	% Reduction at 120 Months
BMI					
Normal (18-25)	7.3 ± 1.4 (CI 95%: 7.1–7.5)	5.9 ± 1.3 (CI 95%: 5.7–6.1)	5.6 ± 1.3 (CI 95%: 5.4–5.8)	-19%	-23%
Overweight (25-30)	8.3 ± 1.4 (CI 95%: 8.1–8.5)	6.7 ± 1.3 (CI 95%: 6.5–6.9)	5.6 ± 1.3 (CI 95%: 5.4–5.8)	-19%	-32%
Obese (30-35)	11.2 ± 1.4 (CI 95%: 10.9–11.5)	7.4 ± 1.3 (CI 95%: 7.1–7.7)	7.6 ± 1.3 (CI 95%: 7.3–7.9)	-33%	-32%



long-term persistence of reduced NSAID consumption throughout a prolonged period of repeated courses of hip VS.

Limitations

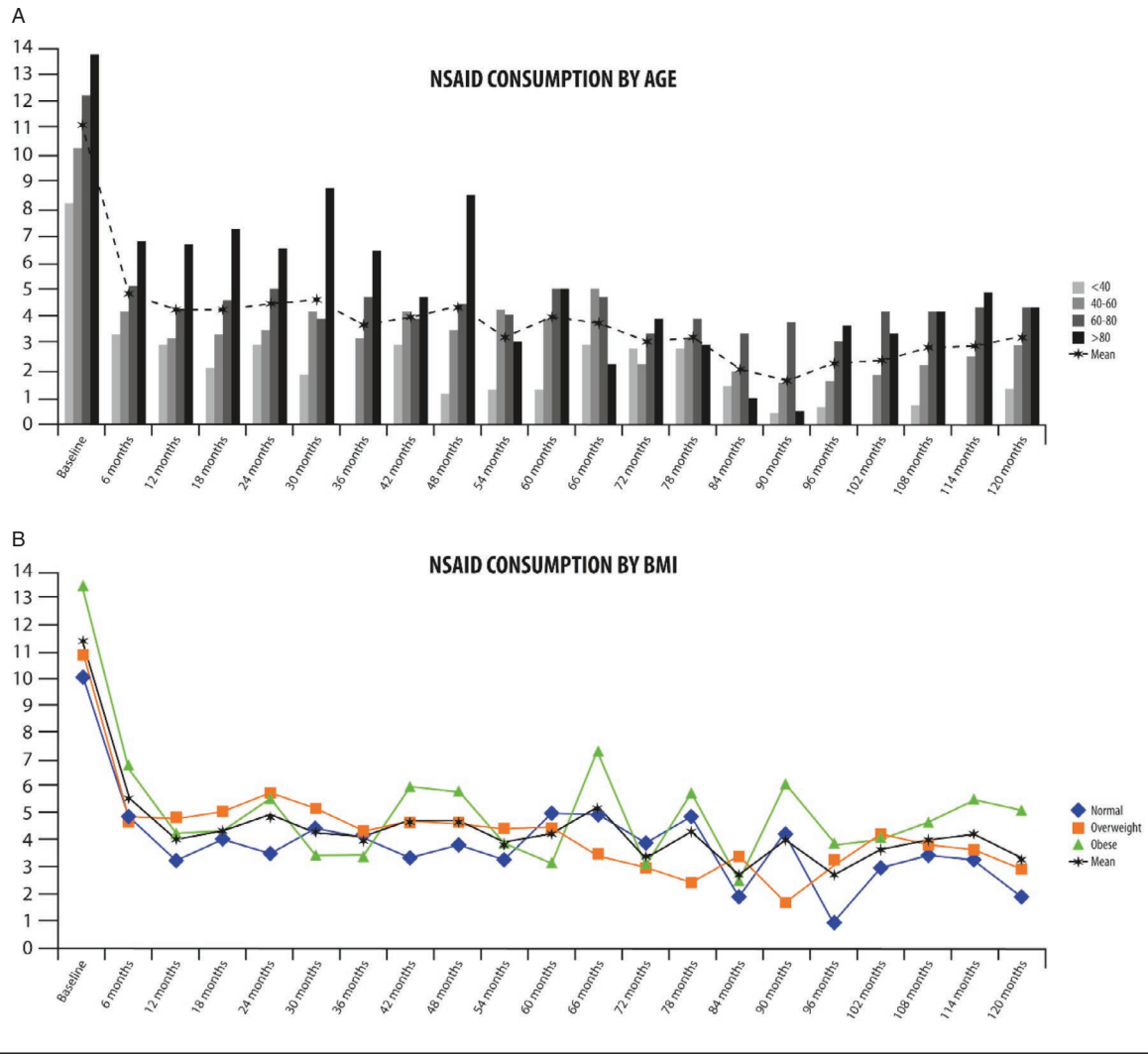
This study has limitations, including the absence of a control group, which poses challenges in clinical practice when conducting long-term follow-up studies of hip pain management. Additionally, confounding factors, such as the use and dosage of symptomatic slow-acting drugs for osteoarthritis, dietary supplements, physical activity, sarcopenia and other non-pharmacological interventions, as well as occupational or sports activities, were not accounted for in the analysis. For example, combining VS with structured physical activity could potentially enhance outcomes compared with VS alone. Furthermore, radiographs were obtained to monitor disease progression and to exclude relevant structural deterioration in patients who showed poor response to treatment or reported worsening symptoms. Therefore, during the follow-up period, radiographic assessments were not standardized across the study population. Patients underwent hip radiographs approximately every 2–3 years at different external radiology centres without centralized acquisition protocols or image reading. Due to the heterogeneity of imaging methods and absence of centralized evaluation, K-L grading or other radiographic classifications were not consistently applied or systematically recorded, and thus radiographic progression data were not deemed reliable for inclusion as an outcome measure in this study, which focused on symptomatic outcomes.

Nonetheless, a dedicated radiological analysis is currently under way and will be reported separately in a forthcoming publication.

Conclusions

This 10-year cohort study corroborates previous findings on the clinical efficacy, safety and reproducibility of IA HyalOne® (4 mL dose) for treating symptomatic hip OA.

Figure 7. NSAID intake over 120 months categorized by (A) age and (B) BMI.



Significant improvements were observed within the first 6 months, and subsequent injections administered every 6 months sustained these benefits, maintaining or even improving efficacy over time. The treatment proved effective across all ages and BMI subgroups and demonstrated that HyalOne® maintains its efficacy with repeated injections. The findings further support the role of US-guided VS as a maintenance therapy for managing hip OA.

Future research should focus on identifying predictors of response to IA HA therapy. Larger, long-term prospective studies are warranted to evaluate its effectiveness in patients with diverse demographics and clinical profiles. Future studies should also incorporate objective outcomes, such as radiographic progression post-treatment or time to THR, to provide deeper insights into the long-term benefits of IA HA therapy.

Supplementary Material available at: https://www.drugsincontext.com/wp-content/uploads/2025/07/dic.2025-3-4-Suppl.pdf

Contributions: Study design: Migliore, A, Boni G; Delucia O; data collection: Massafra U, Iannarelli N, Paglionico A, Giovannangeli F, Grimaldi S; data interpretation: Cunego E, Saporito F, Migliore A; manuscript writing: Migliore A, Cunego E; manuscript editing: All. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Data availability: All data generated or analyzed during this study are included in this published article and its supplementary material.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2025/07/dic.2025-3-4-COI.pdf

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