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Original Research

Liposomal composite gel for knee osteoarthritis: mechanical and physicochemical properties assessment and clinical outcomes of a single-arm prospective study

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ABSTRACT

Introduction

Knee osteoarthritis (OA) impairs joint lubrication and biomechanics, causing pain and functional decline. Hybrid hyaluronic acid-phospholipid systems have shown enhanced boundary lubrication and favorable viscoelastic properties in experimental models, supporting clinical relevance.

Objectives

To evaluate the rheological and tribological properties, safety, and clinical outcomes of a liposomal composite gel in knee OA with a minimum 6-month follow-up.

Methods

This study was conducted in two stages. The first involved the rheological and tribological assessment of the liposomal composite gel using amplitude sweep testing and ball-on-cartilage tribometry. The second was a prospective study of 50 symptomatic patients who received three intra-articular knee injections. Pain and function were assessed using the Visual Analog Scale and the Western Ontario and McMaster Universities OA Index at baseline and at 2, 6, 14, and 28 weeks, with follow-up at 2 years. Objective assessments included Timed Up and Go, Five Times Sit-to-Stand, 10-Meter Walk Test, and Maximal Voluntary Isometric Contraction, which were evaluated up to 28 weeks.

Results

Rheological analysis demonstrated a broad linear viscoelastic region, while tribological testing showed a 13–14% reduction in friction coefficient compared with controls. Pain and stiffness decreased significantly within two weeks ($p \leq 0.01$) and remained improved through 28 weeks and at 2 years ($p \leq 0.0001$). Functional performance and extensor muscle strength improved significantly ($p = 0.008$).

Conclusions

The liposomal composite gel exhibited favorable rheological and tribological properties and resulted in rapid and durable improvements in pain and in knee OA with a favorable safety profile.

Level of evidence

IV.

List of abbreviations in the text

5×STS, Five Times Sit-to-Stand; 10mWT, 10-Meter Walk Test; BMI, Body mass index; G', Storage Modulus; G'', Loss Modulus; HA, Hyaluronic acid; IA, Intra-articular; LVR, Linear viscoelastic region; LAOS, Large-amplitude oscillatory shear; MAOS, Medium-amplitude oscillatory shear; MCID, Minimal clinically important difference; MW, Molecular weight; MVIC, Maximal voluntary isometric contraction; OA, Osteoarthritis; PL, Phospholipids; POPC, 1-palmitoyl-2-oleoyl phosphatidylcholine; SAOS, Small-amplitude oscillatory shear; SD, Standard deviation; SEM, Standard error of measurement; SF, Synovial fluid; TUG, Timed Up and Go; VAS, Visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; $\tan \delta$, Loss factor

Keywords

intra-articular composite; joint lubrication; knee osteoarthritis; liposomal gel; tribosupplementation; viscosupplementation

INTRODUCTION

Degeneration of the synovial joint environment in osteoarthritis (OA) progression significantly disrupts joint biomechanics, compromising lubrication and increasing friction, pain, and functional decline in patients with Kellgren–Lawrence grades II or III.^{1, 2, 3, 4} Progressive alterations in synovial fluid (SF) rheology, mainly related to reductions in hyaluronic acid (HA) concentration and molecular weight (MW), reduce HA's intrinsic ability to provide low friction at the cartilage interface and dissipation of mechanical energy. Collectively, these factors contribute to elevated shear forces at the cartilage surface and accelerated symptom progression.^{5, 6, 7}

HA is a key determinant of joint tribology through its viscoelastic and boundary lubricating abilities, but its structure and turnover are adversely affected in OA joints.^{3, 6, 7, 8} Although intra-articular (IA) HA supplementation can partially restore synovial viscoelasticity and has been associated with sustained pain reduction and functional improvement in OA joints,^{9, 10} emerging evidence indicates that phospholipids (PL) constitute an additional and essential component of effective boundary lubrication.¹¹

Phosphatidylcholines, in particular, interact with hyaluronan and lubricin to form surface-associated structures that lower friction more efficiently than HA alone.^{12, 13, 14, 15} Molecular dynamics and tribological studies demonstrate that the HA-PL combination can facilitate a transition from sliding to rolling motion and exhibit a characteristic slide-to-roll interaction that reduces interfacial shear under physiological loading.^{3, 13, 14, 16, 17} These hybrid systems also display favorable viscoelastic behavior, supporting energy dissipation within relevant deformation ranges.^{13, 14, 16} Collectively, these observations indicate that combining hyaluronan with PL may enhance both boundary lubrication and viscoelastic response in osteoarthritic joints.

Overall, these data indicate that HA-PL hybrid systems may effectively restore joint lubrication and viscoelastic function in OA.^{12, 13, 14, 15, 16, 17} Thus, a liposomal composite gel (Lipotris™, Biovico, Poland) composed of 2.2% HA and liposomes composed of 1-palmitoyl-2-oleoyl phosphatidylcholine (POPC) was developed to leverage these synergistic mechanisms.

The objective of the present study was threefold: (1) to evaluate the rheological and tribological properties of a liposomal composite gel by assessing the linear viscoelastic region (LVR), storage modulus (G'), loss modulus (G''), complex viscosity ($|\eta^*|$), loss factor ($\tan \delta = G''/G'$) and the coefficient of friction (μ), respectively; (2) its clinical safety with continuous monitoring and documentation of adverse events and serious adverse events, and (3) its clinical outcomes in knee OA with a minimum 6-month follow-up, including pain assessment using the visual analog scale (VAS) as primary outcome, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, performance on functional tests, maximal voluntary isometric contraction (MVIC) measurements, and minimal clinically important difference (MCID) for VAS pain and WOMAC as secondary outcomes. Given the exploratory nature of this study, a single-arm design without a control group was adopted to enable detailed longitudinal assessment of clinical outcomes and safety; however, this design limits causal inference and should be considered when interpreting the results.

METHODS

This study was conducted in two stages. The first stage involved the rheological and tribological assessment of the liposomal composite gel. The second stage involved clinical evaluation of the product in the treatment of knee OA. The clinical study was a single-center, single-arm, prospective, unblinded, non-randomized trial conducted in accordance with International Council for Harmonisation Good Clinical Practice and the Declaration of Helsinki from January 2021 to December 2022. All procedures used in this study were approved by the Bioethics Committee of [blinded]. The study has been registered on ClinicalTrials.gov with the identifier: [blinded].

Stage 1. Rheological and Tribological Evaluation of the Liposomal Composite Gel

The rheological and tribological properties of a liposomal composite gel (Lipotris™, Biovico, Poland) were evaluated using a Kinexus Ultra rotational rheometer with a tribology module (KNX2312, Malvern Panalytical, UK).

Rheological measurements were performed using a flat PU20 geometry at 37 °C with a 2 mm gap. An amplitude sweep test was conducted at 1, 2.5, and 5 Hz over a strain range of 0.01–1000% to determine the linear viscoelastic region (LVR).^{18, 19} The storage modulus (G'), loss modulus (G''), complex viscosity ($|\eta^*|$), and loss factor ($\tan \delta = G''/G'$) were recorded.

Tribological testing was conducted using the ball-on-plate attachment. A metal ball–bovine cartilage configuration was used, with additional measurements in a metal ball–metal pin system used to assess the lubricating performance of the tested hydrogel formulation under boundary lubrication conditions, in accordance with methodologies commonly applied to biomimetic hydrogel lubricants.^{20, 21} Tests were performed at 25 °C across 3–16 rad/s ($\approx$ 0.5–2.5 Hz). The liposomal composite gel was compared with bovine SF and HA. The coefficient of friction (μ) was recorded as a function of angular velocity.

Stage 2. Clinical Study

Patient eligibility criteria

Patients with symptomatic knee OA were enrolled at [blinded], in accordance with predefined clinical and radiographic inclusion and exclusion criteria (Table 1). Enrolment included patients with Kellgren–Lawrence grade II–III structural disease, persistent knee pain, and confirmed eligibility after orthopedic examination.

Table 1. Patient eligibility criteria of the prospective clinical trial of a liposomal composite gel in treating knee osteoarthritis.

Inclusion Criteria
• Age between 38 and 70 years
• Diagnosis of osteoarthritis (OA) based on the American College of Rheumatology (ACR) criteria

- Radiographic confirmation of OA, grade II - III according to the Kellgren-Lawrence scale
- Presence of knee joint pain for at least 3 months
- Screening pain intensity in the target knee measured on the Visual Analog Scale (VAS) scale was required to be 4 for the symptomatic knee and 2 for the contralateral knee

Exclusion Criteria

- Previous intra-articular injections of HA or platelet-rich plasma within 6 months, or corticosteroid injections within 3 months before enrollment
- Current joint infection
- History of knee arthroscopy within 1 year prior to examination
- Systemic inflammatory and autoimmune diseases that involve the joint (e.g., rheumatoid arthritis, spondyloarthropathies, systemic lupus erythematosus)
- History of total knee arthroplasty and osteotomy
- Ankylosis of the study joint
- Dermatitis or any dermatological condition at the intended injection site
- Known hypersensitivity to any component of the investigational product
- Coexisting degenerative changes in other lower limb joints (hip, foot)
- Active or past malignancy or other neoplastic disease
- Ongoing oral corticosteroid therapy
- Use of medications affecting blood coagulation (e.g., heparins, oral anticoagulants, thrombolytic drugs)
- Pregnancy or breastfeeding
- History of knee injury, bone fracture, joint dislocation, or other musculoskeletal disorders affecting the study joint
- Participation in other clinical trials

HA: hyaluronic acid; OA: osteoarthritis; ACR: American College of Rheumatology; VAS: Visual Analog Scale.

Liposomal composite gel intra-articular knee injections

The liposomal composite gel is a viscoelastic, opalescent gel intended for use as a tribosupplement in synovial joints. It consists of HA (22 mg/mL) and liposomes formed from POPC (0.8 mg/mL). The composition contains sodium hyaluronate (2.2%), POPC (0.08%), sodium chloride (0.9%), disodium hydrogen phosphate (0.02%), and sodium dihydrogen phosphate (0.005%). It is supplied in 2 mL sterile prefilled syringes, ready for IA administration with a sterile 21G needle.

All eligible patients received three ultrasound-guided (with a high-frequency linear transducer) IA injections of liposomal composite gel at one-week intervals. All injections were performed by a single experienced orthopedic clinician, via a superolateral approach with the patients in the supine position. No local anesthetics were used, nor was joint aspiration performed. Patients were informed to avoid strenuous activity involving the injected joint and limit high-impact exercise for the first 48 hours following each injection.

Outcome measures

The primary outcome was pain assessed using the visual analog scale (VAS). Secondary outcomes included safety (with continuous monitoring and documentation of adverse events and serious adverse events), Western Ontario and McMaster

Universities Osteoarthritis Index (WOMAC) score, performance on functional tests, and maximal voluntary isometric contraction (MVIC) measurements, including associations with demographic and anthropometric factors, including age, sex, body mass index (BMI), and patient satisfaction.^{22, 23} Functional tests included the Timed Up and Go (TUG) test,²⁴ the Five Times Sit-to-Stand (5xSTS),²⁵ and the 10-Meter Walk Test (10mWT).²⁶ All adverse events were coded and categorized using the Medical Dictionary for Regulatory Activities (MedDRA) classification system, ensuring standardized grouping by system organ class and preferred term.

VAS and WOMAC were collected at baseline, and at 2, 6, 14, and 28 weeks after treatment initiation in all scheduled visits through 28 weeks, with an additional follow-up at 2 years ([Supplementary material: Table A1](#)). Functional tests and MVIC were performed according to standardized protocols, at baseline and at 1, 3, and 28 weeks after the third injection ([Supplementary material: Table A2](#)). MVIC was measured using a Forcemeter FB 500 device (AXIS, Gdansk, Poland). Force values were recorded in Newtons and normalized to body weight. Height and weight were measured with a validated medical scale.

Minimal clinically important difference (MCID)

The MCID was calculated to interpret the significance of results. The MCID for pain assessed by VAS was estimated at 0.73 points using the half-standard-deviation (SD) method and at 0.80 points using the standard error of measurement (SEM) method. For the WOMAC total score, the MCID was determined at 9.98 points using the 0.5 SD method and 10.97 points using the SEM method, which aligns with a recent publication.²⁷ The proportion of patients who exceeded the MCID was calculated accordingly. Multiple comparisons against baseline were performed using Dunnett's test.^{18, 28, 29} In addition, anchor-based thresholds derived from Tubach et al.²⁹ were used as conservative reference values to further contextualize the clinical relevance of observed changes.

Sample size calculation

The sample size was determined using VAS pain as the primary outcome. Assuming a clinically relevant 30% reduction in VAS pain and a SD of 35 mm, the required sample size for dependent data with 80% power was estimated at 40 participants. To account for an anticipated 20% dropout during the injection phase, 50 patients were enrolled. Even with an additional 30% dropout during the extended 2-year follow-up, the remaining cohort provided sufficient power for analyses of secondary endpoints.

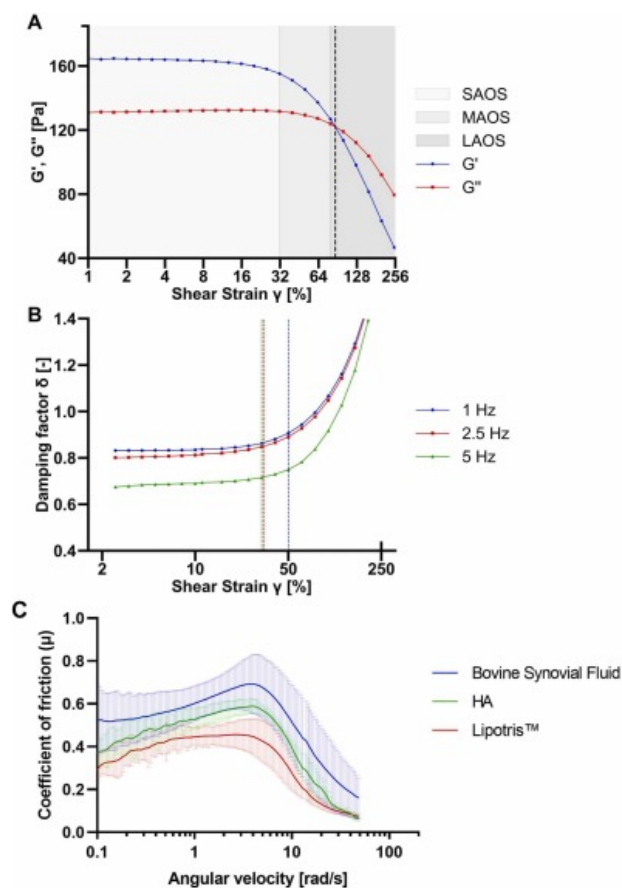
Statistical Analysis

Descriptive statistics were used to summarize the data. Normality of quantitative variables was assessed with the Shapiro-Wilk test. Repeated measures across visits were analyzed using a mixed-effects model with Geisser-Greenhouse correction. Multiple comparisons were performed against the baseline with adjustment for multiple testing. A two-sided $p < 0.05$ was considered statistically significant. Analyses were conducted in accordance with the intention-to-treat principle using GraphPad Prism 9.0.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

Stage 1. Rheological and tribological properties of the Liposomal Composite Gel

In the amplitude sweep tests performed at 1, 2.5, and 5 Hz, the liposomal composite gel exhibited viscoelastic behavior characteristic of a hybrid material. Across all tested frequencies, the material exhibited a broad LVR, consistent with the small-amplitude oscillatory shear (SAOS) regime. The SAOS regime extended to approximately 50% strain at 1 Hz, 25% strain at 2.5 Hz, and 0.1% strain at 5 Hz, within which the elastic modulus G' dominated over the viscous modulus G'' and both moduli remained strain-independent ([Figure 1A](#)).



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Fig. 1. Rheological and tribological characteristics of a liposomal composite gel: (A) Storage modulus (G') and loss modulus (G''). Shaded areas denote SAOS (Small Amplitude Oscillatory Shear), MAOS (Medium Amplitude Oscillatory Shear), and LAOS (Large Amplitude Oscillatory Shear). (B) Damping factor ($\tan \delta = G''/G'$) at 1, 2.5, and 5 Hz with dashed lines marking the estimated limits of the linear viscoelastic region. (C) Coefficient of friction (μ) for the liposomal composite gel, hyaluronic acid (HA), and bovine synovial fluid (SF) across 0.1–100 rad/s. Data are mean $\pm$ SD ($n = 3$).

Beyond the SAOS regime, the material response transitioned into the medium-amplitude oscillatory shear (MAOS) regime, characterized by the onset of nonlinear viscoelastic behavior and a gradual increase in G'' and $\tan \delta$. This transitional MAOS region was observed between the end of the LVR and strain levels of approximately 50%, 33%, and 30% at 1, 2.5, and 5 Hz, respectively.

At higher strain amplitudes, exceeding these values, the liposomal composite gel entered the large-amplitude oscillatory shear (LAOS) regime, as evidenced by a progressive increase in G'' and $\tan \delta$, indicating a shift towards more dissipative behavior under large deformations (Figure 1B).

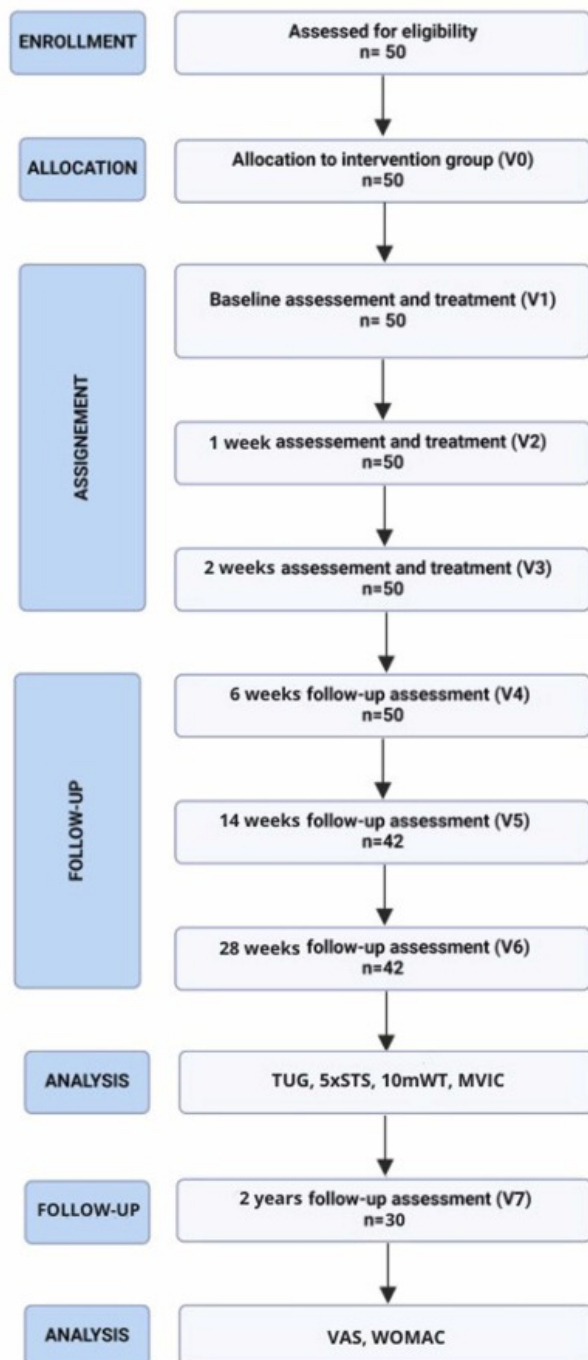
The $\tan \delta$ values increased markedly at approximately 50%, 33%, and 30% strain at 1, 2.5, and 5 Hz, respectively (Figure 1B), indicating a shift from predominantly elastic to more dissipative behavior under large deformations.

Tribological testing showed lower coefficient of friction values for the liposomal composite gel than for native HA hydrogel and bovine SF (Figure 1C). Across the investigated angular velocity range of 0.1–100 rad/s (approximately 0.02–16 Hz), the mean coefficient of friction for the liposomal composite gel was approximately 0.44, compared to 0.50 for the native HA hydrogel, corresponding to a 13–14% reduction in friction. In addition, the overall lubrication performance of the liposomal composite gel differed by approximately 16% from that of the reference samples, indicating enhanced boundary lubrication properties under conditions relevant to physiological joint motion.

Stage 2. Clinical Results

Patients' characteristics

A total of 50 participants were enrolled (mean age 56.7 ± 9.8 years, range: 38–70), of whom 68% were women. The mean BMI was 26.56 ± 8.60 kg/m²; 36% had a BMI within a normal range, 42% were overweight, and 22% obese. Five participants were lost to follow-up or withdrew consent, and three were excluded for using glucocorticoids during the study. Forty-two patients completed 28 weeks of follow-up (82%), and 30 completed 2 years of follow-up (60%) (Figure 2).



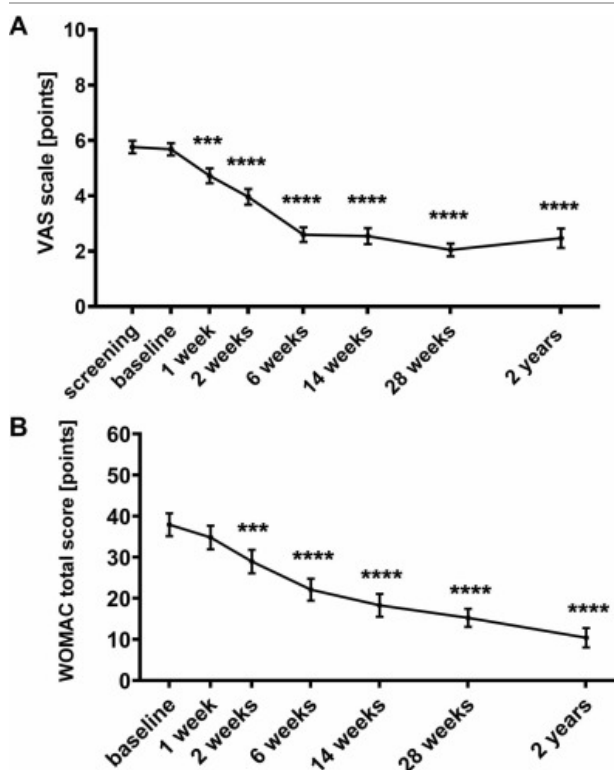
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Fig. 2. Patient flow diagram of a prospective study of the use of a liposomal composite gel for treating knee osteoarthritis.

Patient-reported outcomes

VAS pain decreased significantly two weeks after initiation of the liposomal composite gel therapy (mean 5.5 ± 1.4 to 3.8 ± 1.9 ; $p=0.002$; Figure 3), with further reductions observed during follow-up, reaching the lowest mean value at 28 weeks (2.0 ± 1.5 ; $p<0.001$) and remaining clearly below baseline at the 2-year assessment (2.5 ± 1.9 ; $p<0.0001$). Dunnett's multiple comparisons test demonstrated statistically significant differences versus baseline at all post-treatment visits, with 95% confidence intervals for the mean differences consistently positive, ranging from approximately 0.4 to 1.6 points at early time points and from 2.2 to 4.5 points at later visits. Before and during treatment, women reported higher VAS scores than men, although no sex related differences were observed after therapy, and treatment response was comparable across age and BMI categories.



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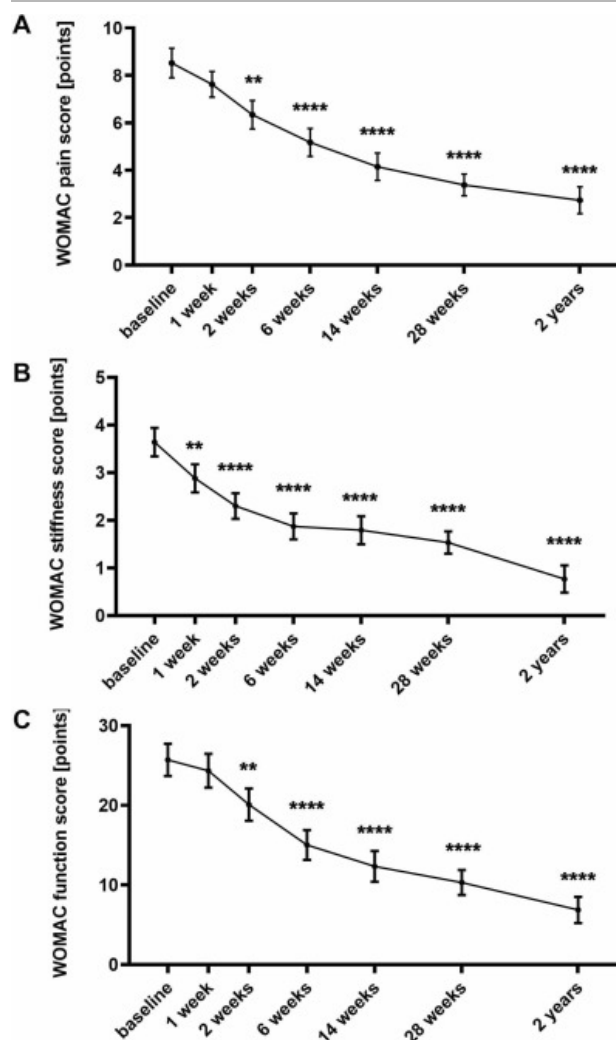
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Fig. 3. Visual Analog Scale (VAS) for pain (A) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores (B) in patients treated with a liposomal composite gel. Error bars show SEM; significance levels: *** $p \leq 0.001$, **** $p \leq 0.0001$.

Consistent with the VAS results, all WOMAC domains showed early and progressive improvement following the liposomal composite gel therapy. The WOMAC total score decreased significantly from baseline to two weeks after therapy (37.8 ± 19.5 to 28.9 ± 20.1 ; $p=0.001$), with further reductions at 6, 14, and 28 weeks, reaching 10.4 ± 12.9 at the 2-year time point ($p<0.0001$; Figure 3).

The WOMAC pain subscore followed a similar pattern, decreasing from 8.5 ± 4.4 at baseline to 6.3 ± 4.2 at two weeks ($p = 0.001$) and continuing to improve through 28 weeks and the 2-year follow-up ($p < 0.0001$; Figure 4A). WOMAC stiffness subscores decreased significantly from week one onward, with sustained improvement observed at all subsequent visits

(Figure 4B). WOMAC physical function also improved progressively, decreasing from 25.7 ± 14.3 at baseline to 20.0 ± 14.3 over two weeks ($p=0.009$), with continued gains throughout the observation period, with the lowest values recorded at 2 years ($p<0.001$) (Figure 4C). Dunnett's multiple comparisons test against baseline showed statistically significant reductions in the WOMAC total score for all post-treatment assessments, with 95% confidence intervals supporting the observed improvement. The earliest improvement was evident within two weeks, with changes of approximately 3 to 15 points in the WOMAC total score across post-treatment time points. Progressively larger differences were observed at later follow-up, reaching approximately 16 points at 28 weeks and 38 points at 2 years.



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Fig. 4. Distribution of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain (A), stiffness (B), and physical function (C) scores in patients treated with a liposomal composite gel. Error bars show SEM; significance levels: ** $p \leq 0.01$, **** $p \leq 0.0001$.

At 14 and 28 weeks post-therapy, 86% of patients reported satisfaction with treatment.

Minimal clinically important difference analysis

The proportion of patients exceeding the MCID on the VAS increased progressively from 64.0% at 1 week to 97.8% at 28 weeks after therapy. Effect sizes grew from moderate (Cohen's $d = 0.61$) at 1 week to very large ($d = 2.29$) at 28 weeks, indicating sustained and clinically meaningful improvement (Supplementary material: Table A3).

The percentage of patients exceeding the MCID on the WOMAC increased from 20.0% at 1 week to 71.1% at 28 weeks. Effect

sizes progressed from small ($d = 0.16$) at 1 week to large ($d = 1.06$) at 28 weeks ([Supplementary material: Table A4](#)).

To further contextualize these findings, anchor-based thresholds were applied as conservative reference values.[30, 31, 32](#) For VAS pain (0–10 scale), using a threshold of 2.0 points, clinically meaningful improvement was achieved by 36.0% of patients at 1 week, 62.0% at 2 weeks, 80.9% at 6 weeks, 81.2% at 14 weeks, 88.9% at 28 weeks, and 80.0% at 2 years. Mean improvements increased from 0.96 ± 1.54 at 1 week to 3.60 ± 1.94 at 28 weeks and remained sustained at 2 years (2.87 ± 2.24). For the WOMAC total score (0–96 scale), with a conservative threshold of 9.1 points, clinically meaningful improvement was achieved by 66.7% of patients at V4 and 71.1% at V5, with mean changes of 20.6 ± 17.5 and 20.4 ± 19.5 points, respectively. Overall, these findings are consistent with distribution-based MCID estimates, supporting the clinical relevance and durability of the observed treatment effects ([Table A5](#)).

Performance on functional tests and isometric evaluations

The mean TUG time was 6.11 ± 1.46 s at baseline ([Supplementary material: Figure A1A](#)) ([Table 2](#)) and improved to 5.58 ± 0.94 s at one month ($p=0.012$). Further improvements were observed at 14 and 28 weeks (5.47 ± 0.87 and 5.53 ± 0.92 s, respectively; both $p < 0.001$).

Table 2. Functional evaluation results of patients treated for knee osteoarthritis with a liposomal composite gel.

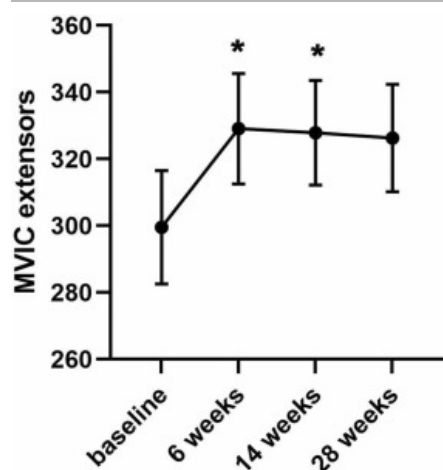
	TUG	5xSTS	10mWT
Before treatment (V1) Follow-ups:	6.11 ±1.46	9.76 ±2.99	5.50 ±1.19
1 month (V4)	5.58 ±0.94 (p=0.012)	8.68 ±1.98 (p=0.067)	5.06 ±0.78 (p=0.019)
3 months (V5)	5.47 ±0.87 (p<0.001)	8.47 ±1.62 (p=0.004)	5.02 ±0.73 (p<0.001)
6 months (V6)	5.53 ±0.92 (p<0.001)	8.34 ±1.61 (p=0.002)	5.09 ±0.78 (p=0.014)

Results are expressed in (mean ± SD; time in seconds). p-values indicate differences vs baseline. Abbreviations: TUG: Timed Up and Go test; 5xSTS: Five Times Sit-to-Stand test; 10mWT: 10-Meter Walk Test; SD: standard deviation.

The mean 5xSTS time decreased from 9.76 ± 2.99 s at baseline to 8.68 ± 1.98 s at one month ($p=0.067$) and to 8.47 ± 1.62 and 8.34 ± 1.61 s at 14 and 28 weeks ($p=0.004$ and $p=0.002$, respectively) ([Supplementary materialFigure A1B:](#)) ([Table 2](#)).

In the 10mWT, mean completion time decreased from 5.50 ± 1.19 s at baseline to 5.09 ± 0.78 s at one month, and remained lower at all post-treatment visits ($p=0.019$, $p < 0.001$, and $p=0.014$ for visits V4, V5, and V6) ([Supplementary materialFigure A1C:](#)) ([Table 2](#)).

A significant increase in extensor muscle strength was observed at one month ($p=0.008$) and continued through six months ($p=0.001$), compared with the baseline MVIC value of 3.7 ± 1.3 N/kg ([Figure 5, Supplementary material: Table A5](#)).



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Fig. 5. Maximal Voluntary Isometric Contraction (MVIC) of knee extensors in patients treated with a liposomal composite gel across visits. Error bars show SEM; significance levels: * $p \leq 0.008$.

Adverse events evaluation

A total of 12 patients (24%) experienced adverse events (AEs) among 50 participants, with all events occurring at low incidence and predominantly mild-to-moderate severity. No AEs were assessed as related to liposomal composite gel, while 2 patients (4%) experienced events considered unlikely related, corresponding to transient injection-site pain. Ten patients (20%) experienced adverse events classified as unrelated. No injection site infections, exudate formation, or systemic reactions were recorded. No serious adverse events or deaths were reported ([Supplementary material: Tables A7 and A8](#)).

Lost to follow-up

Baseline characteristics were compared between the 30 participants who completed the 2-year assessment and the 20 participants who did not ([Table 3](#)). No significant differences were found between groups in baseline VAS pain scores (5.3 ± 1.4 vs. 6.4 ± 1.7 ; $p = 0.070$) or in any other baseline characteristic, including age, weight, height, and sex (all $p > 0.05$). A statistically significant difference in BMI was observed (25.3 ± 4.7 vs. 28.1 ± 4.2 kg/m²; $p = 0.010$); however, BMI was neither an inclusion criterion nor a study endpoint, and baseline pain severity, the primary outcome measure, did not differ significantly between groups.

Table 3. Baseline characteristics of participants who completed vs. did not complete the 2-year assessment after conservative treatment for knee osteoarthritis with a liposomal composite gel for knee osteoarthritis.

Characteristic	Completers (n=30)	Non-completers (n=20)	p-value
Sex (woman), n (%)	18 (60%)	16 (80%)	0.216
Age, years	55.2 ± 10.7	59.0 ± 8.0	0.254
Weight, kg	73.2 ± 16.1	78.8 ± 13.0	0.088
Height, cm	170.0 ± 10.1	167.3 ± 5.4	0.571
BMI, kg/m ²	25.3 ± 4.7	28.1 ± 4.2	0.009
Baseline VAS pain (0-10)	5.3 ± 1.4	6.4 ± 1.7	0.070

Abbreviations: BMI, body mass index; VAS, visual analog scale.

Completers defined as participants with an available 2-year visual analog scale for pain score. Continuous variables are reported as mean $\pm$ SD and compared using the Mann–Whitney U test. Categorical variables are presented as n (%), compared using Fisher's exact test.

DISCUSSION

The main findings of this study is that the presented liposomal composite gel demonstrated favorable rheological and tribological properties, with stable viscoelastic behavior and enhanced lubrication compared to reference samples, and significant and sustained improvements in VAS for pain and WOMAC scores, functional performance, and muscle strength at short-term, with a high proportion of patients achieving clinically meaningful benefits and reporting satisfaction; adverse events were infrequent, mild to moderate, and unrelated to the treatment.

The clinical effectiveness of HA viscosupplementation in OA is well documented.^{31, 32, 33} Increasing evidence also highlights the contribution of PL to synovial lubrication. Molecular dynamics simulations, *in vitro* assays, and *in vivo* studies show that HA-PL systems enhance boundary lubrication and reduce friction more effectively than HA alone, in part by facilitating a transition from sliding to rolling motion and by a slide-to-roll interaction that lowers interfacial shear.^{3, 14, 17} The liposomal composite gel, which combines high-MW hyaluronan with PL-based liposomes, was developed to leverage these synergistic mechanisms by improving both lubrication and viscoelastic damping within the synovial environment, especially in OA, where degraded SF and elevated pro-inflammatory cytokines compromise native lubrication.

The results from rheological and tribological analyses obtained in this study support the formulation concept and its relevance for clinical application. The liposomal composite gel maintained viscoelastic stability within a frequency-dependent linear viscoelastic region. It exhibited increasing G'' and $\tan \delta$ at higher strain amplitudes, consistent with enhanced mechanical energy dissipation under non-linear deformation. This indicates that the liposomal composite gel exhibited stable viscoelastic behavior over a frequency-dependent strain range, with predominantly solid-like properties at low deformation and a gradual transition toward more dissipative, liquid-like behavior at higher strain. Notably, this type of viscoelastic transition is characteristic of native SF under physiological conditions.³⁴ Consequently, this damping capability reduces interfacial shear, thereby favoring stable boundary and mixed lubrication during joint motion. Subsequently, tribological testing revealed a consistently lower coefficient of friction compared to native HA and bovine SF, corresponding to a 13–14% reduction in friction and a 16% improvement in lubrication potential. These characteristics suggest that the formulation reduces shear at the articulating surface and enhances boundary and mixed lubrication. This observation is consistent with the literature, which reports that the HA-PL formulation exhibited a significantly lower coefficient of friction under boundary lubrication conditions than either component alone.^{35, 36, 37}

Surface-sensitive measurements (quartz crystal microbalance and atomic force microscopy) indicated that HA promoted vesicle adsorption and the formation of a continuous, hydrated boundary film, thereby increasing film thickness and shear resistance at the interface.³⁷ Importantly, the lubrication benefit scaled with HA MW and was modulated by ionic composition, with higher MW-HA and the presence of divalent cations enhancing film stability and reducing friction.³⁵ These data support the rationale for selecting a defined HA MW in the liposomal composite gel to ensure effective lubrication and reduced friction during joint movement.

These findings are consistent with contemporary models of joint lubrication described by Jahn and Klein,³ Ruggiero et al.,³⁸ and others,^{13, 14, 15, 16} which emphasize the combined roles of synovial viscoelasticity, PL-mediated boundary lubrication, and biphasic cartilage behavior in maintaining cartilage integrity under load. Within this framework, the mechanical behavior of the presented liposomal composite gel is consistent with the lubrication mechanism described in these models. Notably, the mechanical characteristics of the IA-injected formulation may translate clinically to early symptomatic improvement through smoother motion and reduced stress on the cartilage. It provides a coherent explanation for the rapid reductions in pain and stiffness and the improvements in movement efficiency observed in multiple functional and performance-based outcome measures. Altogether, these findings provide a biomechanical context

for the clinical outcomes discussed below.

The present study demonstrated a rapid and sustained improvement in pain, stiffness, and functional performance following treatment with a liposomal composite gel. Importantly, MCID was achieved by a substantial proportion of patients already within the 1 week following treatment in pain (measured in VAS) and within 2 weeks in overall severity of symptoms in patients with OA (measured in WOMAC total score). These findings were further supported by anchor-based analyses, which confirmed that a substantial proportion of patients achieved clinically meaningful improvement according to externally derived thresholds. Fast therapeutic effect is particularly important in OA, where early pain relief strongly influences patient adherence and perceived treatment value. Interventions that demonstrate early analgesic benefit are more likely to be continued and integrated into routine clinical practice.

The clinical benefits reported here are consistent with those of other viscosupplementation therapies, which are supported by well-documented reductions in pain and improvements in functional status.^{37, 38, 39, 40} However, the present study findings suggest that, if confirmed in comparative trials, a liposomal composite gel IA injection is characterized by an early onset and sustained clinical benefit, with meaningful reductions in VAS and WOMAC scores evident within the first weeks after treatment and maintained for up to 2 years, in contrast to standard HA-based therapy.^{41, 42} Such a distinct clinical benefit of therapy based on liposomal composite gel can be interpreted in the context of the HA-PL combination, which facilitates favorable mechanical conditions within the joint.

More importantly, these observations following liposomal composite gel treatment extend beyond patient-reported outcomes and are reflected in objective assessments of physical function. Specifically, improvements in TUG times reflect enhanced mobility and dynamic balance, whereas shorter 5×STS times indicate enhanced lower-limb functional capacity, which is relevant for functional movement tasks. Faster performance on the 10-Meter Walk Test suggests improved gait efficiency, indicating a less compensatory walking pattern, which is relevant to physiological cartilage loading, a key consideration in the mechanical aspect of OA progression.⁴³ Furthermore, consistent with the observed improvements in functional mobility and gait, increased extensor MVIC may reflect improved neuromuscular activation associated with reduced pain and improved joint loading.⁴⁴

These objective functional measures provide complementary context for the clinical outcomes observed following IA injection of the liposomal composite gel. Furthermore, by facilitating such comprehensive clinical and functional improvements, treatment with a liposomal composite gel may support earlier and more effective participation in rehabilitation and physical activity. This remains highly important, given the growing evidence that early and sustained physical activity is a key component of OA management.⁴⁵

Taken together, the results of this study highlight the relevance of restoring physiological joint lubrication through IA therapy as a basis for interpreting its therapeutic profile, including onset, durability, and functional outcomes. To our knowledge, this is the first clinical study to integrate detailed tribological characterization with a broad panel of clinical outcomes for an IA-injected HA-PL formulation, thereby supporting a translational link between joint lubrication research and routine clinical practice.

The primary limitations of this study are the lack of a control group, blindness, and randomization, which would help differentiate treatment effects from placebo response and reduce potential reporting and assessment bias. However, this reflects the study's primary focus on the longitudinal characterization of the clinical and functional profiles and safety of IA therapy, rather than on comparative efficacy assessment. Loss to follow-up at the 2-year assessment reflected the extended monitoring period, which is commonly associated with lower participant retention in long-term studies. Both groups (those who completed the 2-year follow-up period and those lost to follow-up) were clinically comparable at baseline and were unlikely to have introduced meaningful bias in the reported outcomes. Lastly, MCID has inherent limitations⁴⁶, and the method implemented in our study does not escape them; therefore, careful interpretation is encouraged, especially when referring to VAS values. Future randomized, comparator-controlled studies, ideally incorporating imaging and biomarker-based assessments, will be important for determining whether improvements in joint lubrication have a direct effect on OA joint structure and whether such an effect contributes to sustained clinical

benefit.

CONCLUSION

In summary, the liposomal composite gel exhibited favorable rheological and tribological properties, with stable viscoelastic behavior and enhanced lubrication relative to the reference samples. IA therapy with a liposomal composite gel resulted in rapid and durable reductions in pain and stiffness, as well as improvements in mobility and muscle performance, in individuals with knee OA and demonstrated a favorable safety profile.

Ethics statement

All study procedures were approved by the Bioethics Committee of Poznan University of Medical Sciences (no. 296/2020).

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CRediT authorship contribution statement

Conceptualization: PB. Methodology: PB and PK. Validation: PB. Formal analysis: PB. Investigation: PB and JK. Resources: PB. Data curation: PB, KBZ, and TMF. Writing—original draft preparation: PB, JK, and KBZ. Writing—review and editing: PB, JK, PB, PK, TP, and TMF. Supervision: PB, TP, and TMF. Project administration: PB.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Pawel Bakowski reports a relationship with Biovico Sp Z O O that includes: speaking and lecture fees and travel reimbursement. Theodorakys Marin Fermin reports a relationship with International Cartilage Regeneration & Joint Preservation Society that includes: board membership, consulting or advisory, and travel reimbursement. The author, Theodorakys Marín Fermín, is an Associate Editor for the Journal of Cartilage Repair & Joint Preservation. Given his role, he had no involvement in the peer review of this article and no access to information about it. Full responsibility for the editorial process for this article was delegated to another journal editor. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Conflict of interest disclosure

Pawel Bakowski reports a relationship with Biovico Sp Z O O that includes: speaking and lecture fees and travel reimbursement. Theodorakys Marin Fermin reports a relationship with International Cartilage Regeneration & Joint Preservation Society that includes: board membership, consulting or advisory, and travel reimbursement. The author, Theodorakys Marín Fermín, is an Associate Editor for the Journal of Cartilage Repair & Joint Preservation. Given his role, he had no involvement in the peer review of this article and no access to information about it. Full responsibility for the editorial process for this article was delegated to another journal editor. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work

reported in this paper.

Patient consent statement

Written informed consent was obtained from all patients by the principal investigator before initiation of study-related procedures.

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N/A.

For clinical trials (if applicable)

The study was registered on ClinicalTrials.gov under the identifier NCT06433492.

Informed Patient Consent

The author(s) should confirm that written informed consent has been obtained from the involved patient(s) or if appropriate from the parent, guardian, power of attorney of the involved patient(s); and, they have given approval for this information to be published in this case report (series).

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Complete written informed consent was obtained from the patient for the publication of this study and accompanying images.

Appendix A. Supplementary material

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Supplementary material

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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