Modification of cardiovascular risk factors after viscosupplementation with hyaluronic acid in patients with symptomatic hip and knee osteoarthritis

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Abstract

Objective

We aimed to evaluate the modification of cardiovascular risk factor parameters after intra-articular injection with hyaluronic acid in patients with symptomatic hip and knee osteoarthrtitis. This was a retrospective cohort study of 101 patients meeting the clinical and radiological criteria of the American College of Rheumatology for hip and knee osteoarthritis, Kellgren-Lawrence grades I-IV.

Methods

Patients received four intra-articular injections of hyaluronic acid in the knee and/or hip in the period of study. After the injections, changes in weight and BMI, pain using the visual analogue scale, consumption of pain medications, and physical activity were recorded at each follow-up visit. Analytical variations in blood glucose, HbA1c, total cholesterol, LDL, HDL, and triglycerides were also evaluated.

Results

Over the 24-month study period, weight and BMI were stabilised. A reduction in pain of 1.2 points ($p<0.001$), a 20,76% reduction in analgesic consumption ($p<0.001$), and a 19.81% increase in physical activity ($p<0.001$) and a 21.8% increase in frequency ($p=0.001$) were observed. Total cholesterol ($p=0.002$), LDL ($p=0.009$), HDL ($p=0.023$), and triglycerides ($p=0.021$) showed a significant decrease in all cases when analysed in patients whose baseline levels were pathological.

Conclusion

Intra-articular viscosupplementation with hyaluronic acid in symptomatic hip and knee osteoarthritis achieves a decrease in pain, potentially allowing patients to increase their physical activity levels, which helps control weight and BMI. Secondarily it could influence the improvement of CVRF analytical outcomes in the medium term in those patients who had altered levels.

Key words

knee osteoarthritis. hip osteoarthritis. hyaluronic acid. viscosupplementation. cardiovascular risk factors

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Introduction

Osteoarthritis is the most prevalent disorder affecting the hip and knee in individuals over 60 years of age. It is characterised by the gradual degradation of cartilage tissue and the development of focal osteonecrosis in the subchondral bone. Functionally, it limits the ability to stand and walk, promoting a sedentary lifestyle that increases the incidence of metabolic and cardiovascular diseases due to physical inactivity and subsequent weight gain. This weight gain, in turn, further accelerates cartilage degeneration (1).

Managing this condition poses a significant healthcare challenge, encompassing a spectrum of treatments ranging from conservative approaches to surgical intervention. Non-pharmacological strategies form the cornerstone of care (2). Among these, chondroprotective agents, postural hygiene practices, joint protection techniques, and guided physical activity play essential roles in slowing disease progression.

It is well established that osteoarthritic joints exhibit a decrease in both the concentration and molecular weight of hyaluronic acid (HA). Intra-articular viscosupplementation with HA serves as a therapeutic strategy intended to delay the need for more invasive treatments in patients with moderate symptomatic radiographic stages. This intervention is already well integrated into routine clinical practice (3-5). The resulting reduction in pain and improved joint mobility, due to restoration of synovial viscoelastic properties, translate into increased patient functionality.

There is growing evidence that more severe osteoarthritic involvement of the hip and knee is associated with an increased risk of cardiovascular events (6-9). The pain and physical limitations imposed by hip and knee osteoarthritis often lead to a sedentary lifestyle, which contributes to obesity, a key factor in both the worsening of cardiovascular risk and the progression of osteoarthritis (10-11). These two conditions, osteoarthritis and cardiovascular disease, share common pathways beyond biomechanics, involving biochemical and metabolic interactions, which justify further exploration (12).

Understanding the link between osteoarthritis and cardiovascular risk factors (CVRF), and their impact on patient morbidity and mortality, should encourage a broader perspective in therapeutic goals. Viscosupplementation with HA may help interrupt the cycle of pain, sedentary, behaviour, and weight gain, offering patients the possibility of resuming physical activity. This, in turn, may contribute to better weight management, reduced joint load, and improvements in CVRFs.

The limited of data currently available regarding the impact of intra-articular HA injections on CVRF in patients with symptomatic hip and knee osteoarthritis provide the rationale for this study. Therefore, the objective of this study was to evaluate whether intra-articular HA injections in patients with symptomatic hip and knee osteoarthritis can contribute to improvements in cardiovascular risk factors profiles, including metabolics parameters, body weight, and physical activity levels.

Methods

Study design and data sources

We conducted a retrospective cohort study to evaluate changes in CVRF in patients with symptomatic knee and/or hip osteoarthritis who received intra-articular injections of HA. Laboratory values were obtained from the electronic medical records of routine primary care follow-up visits across a 24-month period.

Although this is an observational study embedded in routine clinical practice, each patient served as their own control in a before-and-after observational design. This follow-up period was chosen to allow adequate time for changes in clinical and laboratory parameters to manifest.

Participants

A retrospective consecutive sampling approach was used. Patients were selected from the registry of individuals who received intra-articular HA injections at our hospital between June 2015 and December 2020. From a total 598 patients, those who met the following inclusion criteria were enrolled: at least two HA injections in the knee and/or

hip, availability of laboratory test results both prior to and after the injection period, and a minimum of 24 months of follow-up. No formal sample size calculation was performed, as this was an exploratory retrospective study. The final sample was based on data availability and adherence to predefined inclusion/exclusion criteria. Exclusion criteria included: patients without appropriate or timely laboratory tests, and those who had undergone surgical procedures on the treated joints prior to inclusion.

Variables

Descriptive variables included: age (continuous), sex assigned at birth (male/female), and affected joint(s) (knee/hip/both). Primary variables (all continuous) comprised fasting glucose, HbA1c, total cholesterol, LDL, HDL, triglycerides, weight, height and body mass index (BMI). Secondary variables included: previous diagnosis of diabetes mellitus (yes/no), Kellgren-Lawrence radiographic grade (I–IV), pain on the visual analogue scale (VAS), use and frequency of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) (yes/no; none/1–3x month/1–2x week/daily), physical activity (yes/no), and frequency of physical activity (none/1–2x week, 3–4x week/daily).

Variables were recorded at baseline (T0), and every 6 months after subsequent injections (T1, T2, T3), until the final 24-month follow-up (T4) (Figure 1). Data were extracted from the regional electronic health record system (DRAGO). Patient data were anonymised and entered into a Microsoft Excel database for analysis.

Interventions

Participants were positioned in a supine position, and the skin overt the injection was carefully sterilised. After aseptic preparation, ultrasound-guided injections were administered. For the hip, the injection was performed via an anterior infrainguinal approach using an 88 mm, 21-gauge needle, directed toward the articular recess of the joint with an in-plane technique (Canon Xario™ 100, Canon Medical System.) (Fig. 2). For the knee, the injection was directed into the suprapatellar articular recess through a superolateral in-plane approach (Fig. 3). In both cases, 4 mL of 15 mg/mL HA (Hyalone®, 60 mg/4mL at 1.5%, molecular weight: 1500-2000 kDa, Fidia Farmaceutici S.p.A.) was injected.

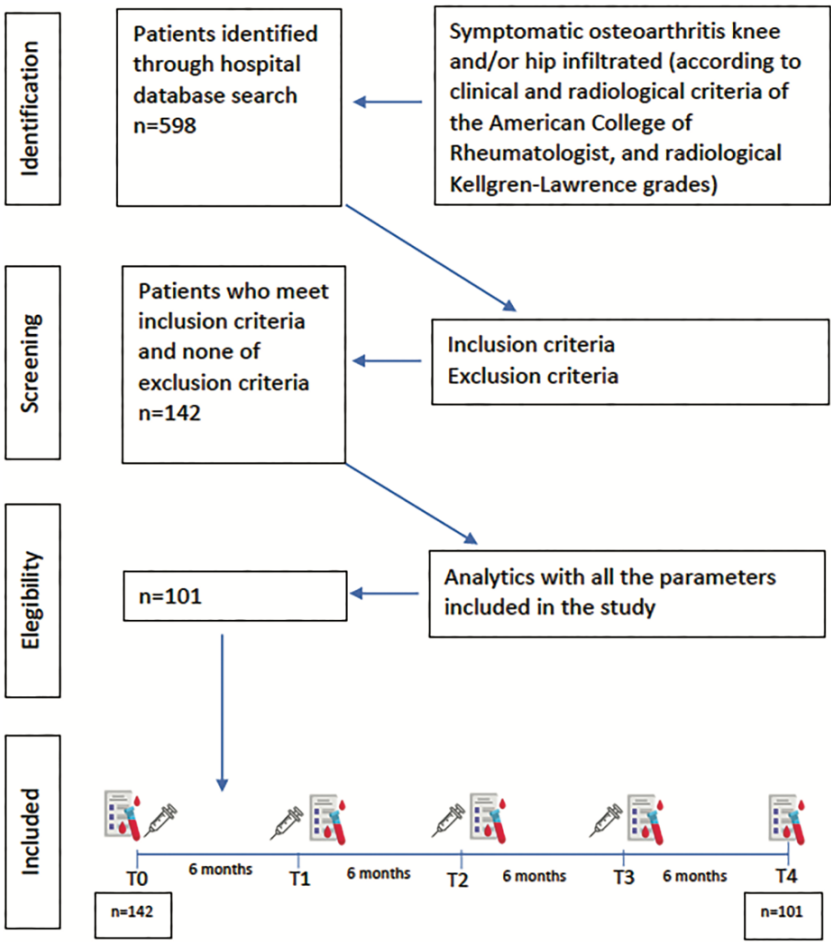

Fig. 1. Summary of the patient selection process and study follow-up.

All procedures were performed by the same physician, who had over 10 years of experience in ultrasound-guided injections. Each patient received four injections per affected joint during the follow-up period. At each visit, height and weight were recorded, and patients completed the questions and questionnaires corresponding to the study variables. Retrospectively, the medical history of each patient was reviewed to identify a blood tests with the relevant parameters: one prior the first injection, one at 24 months, and any available intermediate tests.

Statistical methods

Descriptive analyses were conducted according to the nature of the variables described above. Normality of continuous variables was assessed using the Shapiro-Wilk test to determine the appropriate statistical test. Changes observed after two years of intervention and follow-up were evaluated using paired-sample inferential statistics, based on the type of variable: categorical variables were analysed with McNemar's chi squared test, and quantitative variables with Student's t-test or Wilcoxon test, as appropriate. Additionally, a General Linear Model for repeated measures was applied. All statistical tests were two-tailed, and the significance level for rejecting the null hypothesis of no intervention effect was set at 5% ($p<0.05$). All analyses were performed using SPSS (IBM SPSS Statistic for Windows, v. 22.0; IBM Corp).

Results

Out of the 598 patients who received intra-articular HA injections for symptomatic osteoarthritic of the hip and/or

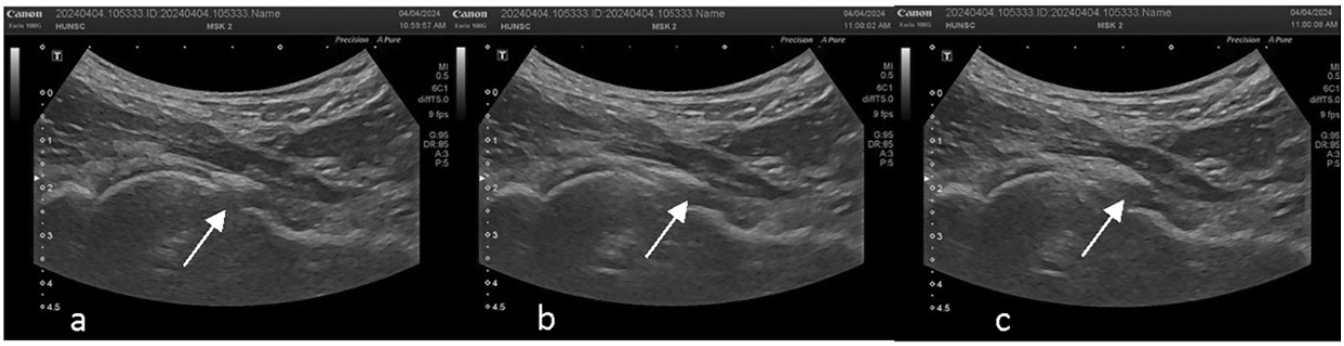

Fig. 2. Images of ultrasound-guided infiltration of the hip, in-plane anterior approach with sequence of hyaluronic acid entry into the hip joint capsule at the level of the cervical projection of the hip a, b and c.

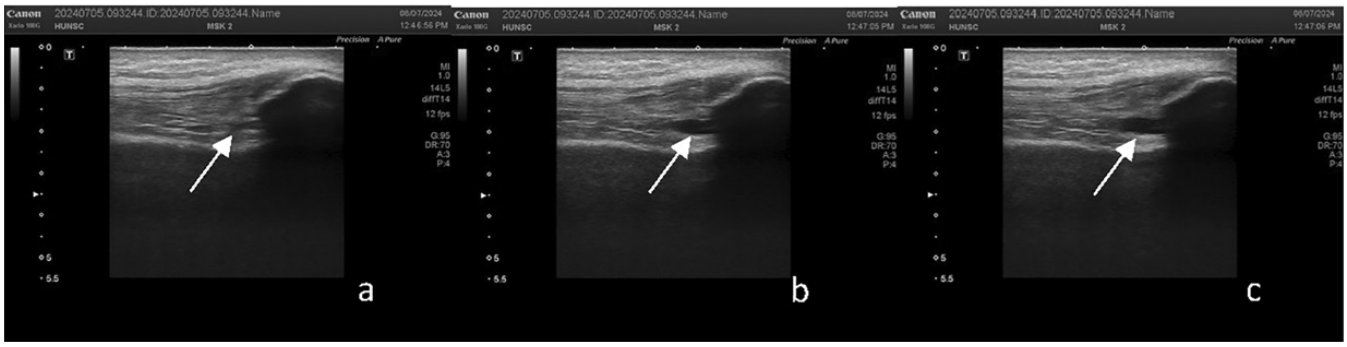

Fig. 3. Ultrasound image of infiltration of the knee by lateral, out-of-plane approach in superexternal recess and filling of the recess with hyaluronic acid **a**, **b** and **c**.

knee, 141 met the inclusion criteria and none of the exclusion criteria. Among these, 101 patients had blood test results that included all study variables at each follow-up and were therefore included in the final analysis. The mean age was 66.54±12.13 years, ranging from 25 to 88 years, and 77.2% were women. Injections were administered to the hip in 30.7% of cases, to the knee in 67.3%, and to both joints in 2%. Viscosupplementation was bilateral in 65.3% of patients and unilateral in the remainder. Regarding radiological osteoarthritis severity, grade II was the most prevalent in both knee and hip. The mean height was 165.0±9.7 cm. Additionally, 55.4% of patients had a prior diagnosis of diabetes mellitus (Table I).

Table I. Patients' characteristics.

Variables n=101				
Assigned sex (at birth) (n (%))				
Females	78 (77.2)			
Males	23 (22.8)			
Age (mean± SD)	66.54 (12.13)			
Affected joints (n (%))				
Hip	31 (30.7)			
Knee	68 (67.3)			
Hip and knee	2 (2.0)			
Laterality (n (%))				
Unilateral	35 (34.7)			
Bilateral	66 (65.3)			
Infiltrated joints (n)				
Total	232			
Knees	82			
Hips	150			
Lawrence-Kellgren grades (%)	**I**	**II**	**III**	**IV**
Knee R (n=58) (57.4%)	10.9	31.7	11.9	3.0
Knee L (n=62) (41.4%)	8.9	35.6	13.9	3.0
Hip R (n=29) (38.7%)	2.0	15.8	5.9	5.0
Hip L (n=23) (32.8%)	4.0	11.9	5.0	2.0
Height (mean ± SD)	165.01 (8.73)			

Height expressed in cm. SD: standard deviation; R: right; L: left.

Weight/BMI

At baseline, the average BMI of the study population was in the overweight range, with 29.53 ± 5.32. Over the 24-month follow-up, a mean weight reduction of 1.79 kg was observed, although this change was not statistically significant (p=0.45). When evaluating the evolution of BMI across the five measurement points, a decreasing trend was noted, with a non-significant reduction of 0.62 points between the first and final measurements (p=0.42).

A subgroup analysis was conducted in patients with a baseline BMI >25 to assess weight and BMI changes specifically among those who were overweight at the start of the study. In both cases, values remained stable throughout the follow-up, with no statistically significant increase or decrease ob-

Table II. Clinical variables at baseline and after each infiltration.

Variables	Baseline (T0)	6 months (T1)	12 months (T2)	18 months (T3)	24 months (T4)	*p* value*
Weight (mean ± SD)	80.41 (15.06)	79.67 (14.49)	79.16 (13.80)	79.39 (13.98)	78.62 (14.01)	0.45
Weight in patients with baseline BMI >25	82.48 (12,61)	81.55 (11.98)	81.34 (11.56)	81.87 (11,41)	81.44 (11,83)	0.38
BMI (mean ± SD)	29.53 (5.32)	29.29 (5.09)	29.10 (4.83)	29.20 (4.99)	28.91 (4.94)	0.42
Baseline BMI >25	30.86 (4.31)	30.49 (4.04)	30.37 (4.03)	30.66 (4.18)	30.66 (4.18)	0.36
VAS (mean ± SD)	5.5 (2.10)	5.01 (2.14)	4.75 (2.34)	4.77 (2.21)	4.30 (2.67)	**<0.001**
VAS grades, n (%)						
None (0)	2 (2.0)	4 (4.0)	5 (5.0)	6 (5.9)	13 (12.9)	
Mild (1-5)	52 (51.5)	55 (54.5)	52 (51.5)	56 (55.4)	52 (51.5)	
Moderate (6-7)	25 (24.8)	29 (28.7)	27 (26.7)	25 (24.8)	24 (23.8)	
Severe (>7)	22 (21.8)	13 (12.9)	17 (16.8)	14 (13.9)	12 (11.9)	**0.037**
Intake of analgesic, n (%)						
Yes	75 (74.26)	66 (65.3)	67 (66.3)	62 (61.39)	54 (53.5)	
No	26 (25.74)	35 (34.7)	34 (33.7)	39 (38.6)	47 (46.5)	**<0.001**
Intake frequency, n (%)						
None	26 (25.7)	35 (34.7)	34 (33.7)	39 (38.6)	47 (46.5)	
1–3 times/month	14 (13.9)	16 (15.8)	21 (20.8)	22 (21.8)	17 (16.8)	
1–2 times/week	21 (20.8)	28 (27.7)	23 (22.8)	23 (22.8)	21 (20.8)	
Every day	40 (39.6)	22 (21.8)	23 (22.8)	17 (16.8)	16 (15.8)	**<0.001**
Physical activity, n (%)						
Yes	71 (70.29)	78 (77.2)	80 (79.2)	84 (83.2)	90 (90.1)	
No	30 (29,71)	23 (22.8)	21 (20.8)	17 (16.8)	11 (9.9)	**<0.001**
Frequency of physical activity, n (%)						
None	30 (29.7)	23 (22.8)	21 (20.8)	17 (16.8)	10 (9.9)	
1–2 times/week	44 (43.6)	36 (35.6)	31 (30.7)	30 (29.7)	23 (22.8)	
3–4 times/week	19 (18.8)	31 (30.7)	36 (35.6)	36 (35.6)	38 (37.66)	
Every day	8 (7.9)	11 (10.9)	13 (12.9)	18 (17.8)	30 (29.70)	**0.001**

Weight expressed in kg. SD: standard deviation; BMI: body mass index; VAS: visual analogue scale.
*p-value for paried test between basal time and 24 months.

served (p=0.38 and p=0.36, respectively) (Table II).

Pain

A progressive reduction in pain, as measured by the VAS, was observed over the course of the study. The mean baseline score was 5.5±2.1, which decreased to 4.30±2.67 at the final follow-up, representing an average reduction of 1.2 points (21.8%), with p<0.001 (Fig. 4).

When stratifying pain intensity into four VAS categories, a notable decrease was seen in the proportion of patients reporting severe pain (VAS >7), which declined from 21.8% at baseline to 11.9% at follow-up (p=0.037). No relevant changes were observed in the remaining categories (Table II).

Analgesia

When comparing analgesic use between the first visit and the final follow-up, the proportion of patients reporting use decreased from 74.3% to 53.5%, representing a total reduction of 20.76% (p<0.001). Among those who initially used analgesics, 33.3% reported no longer using them at 24 months (Fig. 4, Table II).

Regarding the frequency of analgesic use, daily consumption decreased by 23.8% – from 39.6% to 15.8% – while the proportion of patients who reported never using analgesics increased by 20.8% (p<0.001) (Table II).

Physical activity

At baseline, 71 participants (70.3%) reported engaging in physical activity. After completing the full HA injection protocol and follow-up visits, this proportion increased to 90 individuals (90.1%), representing an absolute increase of 19.8 percentage points (p<0.001). Among those who were initially inactive, 73.3% began engaging in some form of physical activity.

When analysing the frequency of physical activity, the proportion of individuals who reported no activity declined from 29.7% at baseline to 9.9% at final visit (-19.8%). There was also a decrease in the group exercising 1–2 times per week (-20.5%), while the proportions of those exercising 3-4 times per week and daily increased by 18.8% and 21.8%, respectively (p=0.001). Only 8 out of the initial 101 patients continued to report no physical activity at the end of follow-up (Table II).

Blood glucose

The comparison between baseline and final mean blood glucose levels showed a minimal change of -0.59 mg/dL, which was not statistically significant (p=0.885). In the subgroup of patients with baseline glucose levels >100 mg/dL, a downward trend was observed, with an average decrease of 9.79 mg/dL (p=0.090) (Table III, Fig. 5).

Regarding glycated hemoglobin (HgA1c), patients with baseline values >6 mg/dL were analysed. The means HbA1c decreased from 7.07±1.40 mg/dL at baseline to 6.82±0.89 mg/dL at the fourth follow-up, resulting in a difference of 0.25 mg/dL, which was not statistically significant (p=0.253).

Total cholesterol

A comparison of paired samples

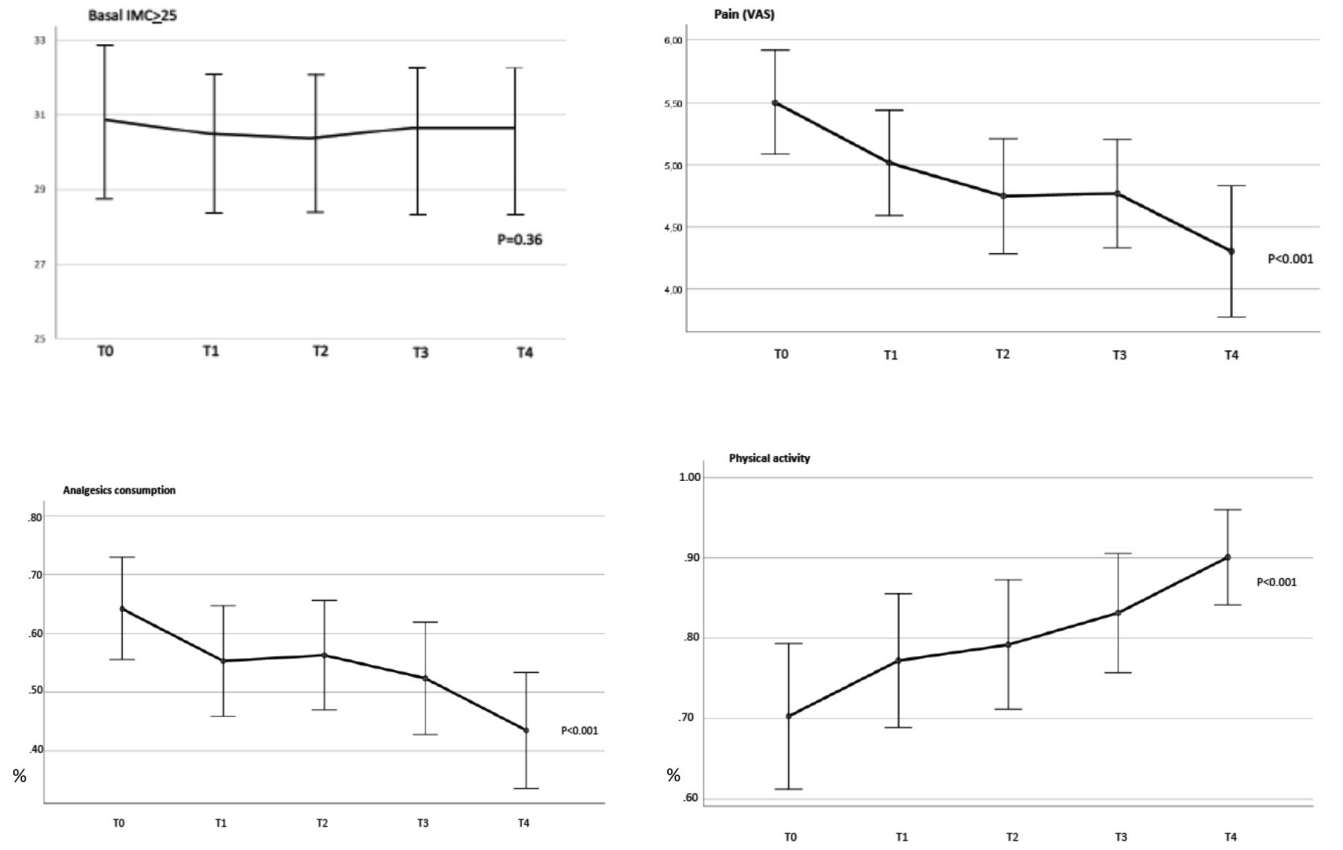

Fig. 4. Modification of clinical variables in each control.
T0: time of 1st injection and first analytical results; T1: time 6 months after 2nd injection; T2: time 6 months after 3rd injection; T3: time 6 months after 4th injection; T4: time 6 months after 5th injection; VAS: visual analogue scale.
Mean values ± standard deviations. The level of statistical significance was set at a *p*-value <0.05.

showed no significant difference in mean total cholesterol levels between baseline (193.27±41.17 mg/dL) and the final follow-up (194.09±36.68 mg/dL), with a mean change of -0.82 mg/dL (p=0.932).

However, when applying a threshold of >200 mg/dL to define elevated total cholesterol, 43.4% of patients met this criterion at baseline. In this subgroup, the mean total cholesterol level decreased from 239.48 mg/dL to 218.24 mg/dL, representing a reduction of 21.24 mg/dL (95% CI: 8.35 to 34.37), which was statistically significant (p=0.002) (Table III, Fig. 5).

LDL cholesterol

A comparison of paired samples showed a mean LDL cholesterol level of 109.80±34.32 mg/dL at baseline and 106.80±31.84 mg/dL at the final follow-up, resulting in a non-significant difference of 3 mg/dL (p=0.361).

In the subgroup of patients with base-

Table III. Baseline and post infiltration analytical variables.

Variables	Baseline (T0)	6 months (T1)	12 months (T2)	18 months (T3)	24 months (T4)	*p*-value*
Basal glycaemia >100 n=34 (33.3%)	138.14 (38.44)	131.83 (35.12)	133.35 (37.89)	133.97 (37.74)	128.35 (20.72)	0.09 0
Basal glycaemia <100 n=67 (63.3%)	90.03 (6.56)	92.50 (8.96)	97.58 (16.82)	96.00 (11.31)	99.47 (14.76)	**0.001**
HgAc1>6 n=23 (22.8%)	7.07 (1.403)	7.22 (1.96)	6.42 (0.97)	6.69 (0.92)	6.82 (0.89)	0.253
Basal cholesterol ≥200 n=44 (43.4%)	239.48 (43.4)	222.57 (28.74)	218.57 (38.51)	225.05 (28.26)	218.24 (40,15)	**0.002**
Basal cholesterol <200 n=57 (56.6%)	171.04 (22,61)	175.98 (31.34)	178.42 (40.56)	174.77 (28.44)	182.30 (33.55)	0.013
Basal LDL ≥110 n=37 (36.63%)	139.21 (22.20)	129.61 (26.86)	127.54 (31.37)	127.71 (29.10)	123.36 (25.40)	**0.009**
Basal LDL <110 n= 64 (63.37%)	84.06 (16.37)	84.60 (21.84)	87.81 (32.219)	86.87 (19.67)	92.31 (27.13)	0.155
B Basal HDL ≥40 n=72 (86.14%)	59.72 (14.18)	60.43 (15.80)	60.06 (15.90)	59.21 (15.10)	60.98 (15.42)	0.247
Basal HDL <40 n=14 (13.86%)	34.57 (1.99)	36.86 (4.98)	37.71 (4.46)	36.43 (4.61)	38.29 (3.63)	**0.023**
B Basal TG ≥150 n=20 (19.80%)	211.07 (50.19)	183.13 (66.87)	184.53 (61.49)	175.33 (57.95)	172.33 (63.45)	**0.021**
B Basal TG <150 n= 81 (80.20%)	93.57 (24.36)	108.40 (41.77)	103.38 (45.74)	111.06 (47.57)	115.02 (38.69)	0.001

Values are expressed as means ± standard deviation. Units in mg/dL.
LDL: cholesterol low density lipoprotein; HDL: cholesterol high density lipoprotein; TG: triglycerides.
*p-value (statistics from general linear model repeated measure).

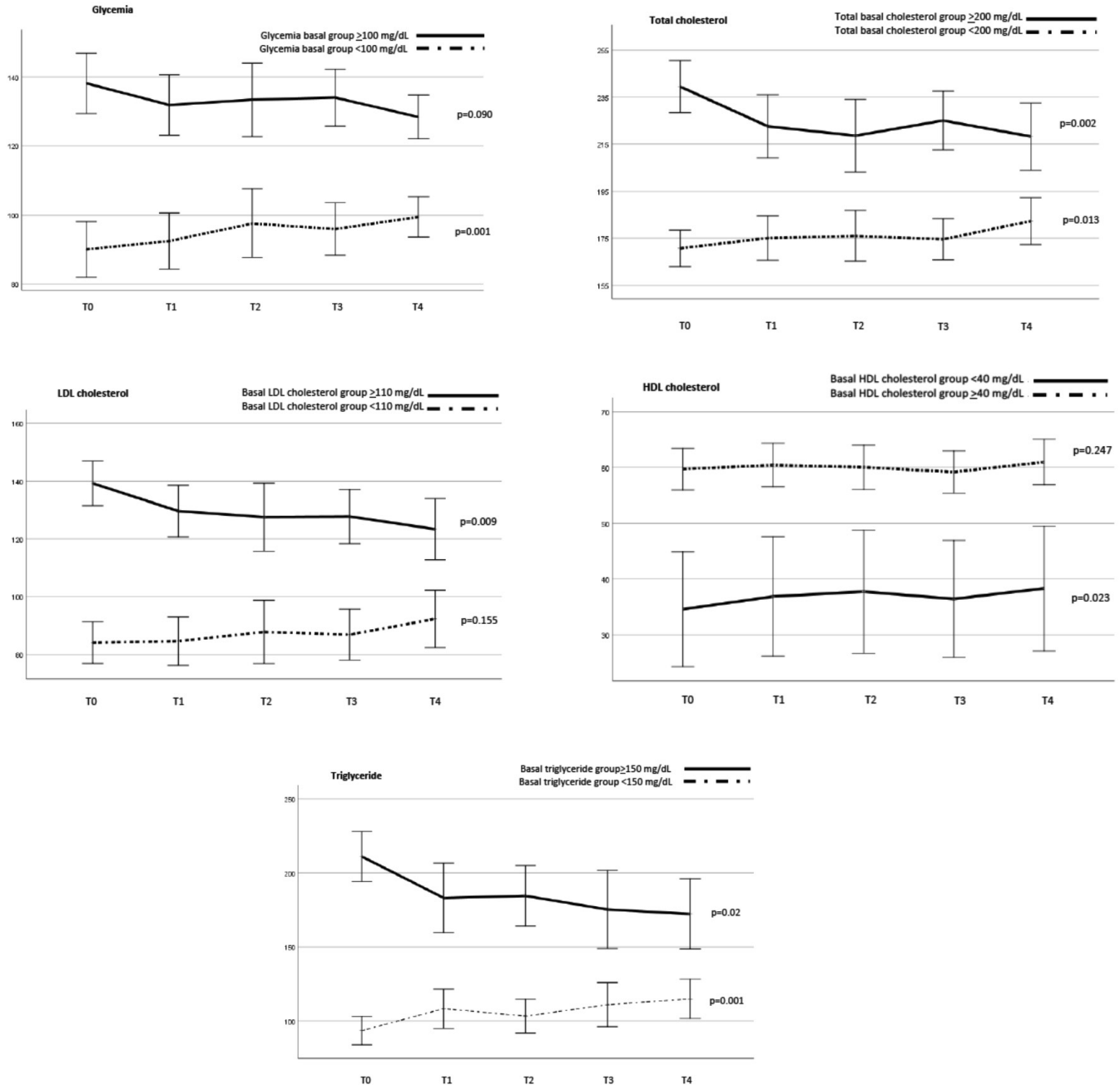

Fig. 5. Improvement of analytical parameters in each control.
T0: time of 1st injection and first analytical results; T1: time 6 months after 2nd injection; T2: time 6 months after 3rd injection; T3: time 6 months after 4th injection; T4: time 6 months after 5th injection.
Mean values ± standard deviations. The level of statistical significance was set at a *p*-value <0.05.

line LDL cholesterol >110 mg/dL, a significant average reduction of 16.69 mg/dL was observed at 24 months (95% CI: 4-27 mg/dL, *p*=0.009). This reduction began at the six months follow-up and was maintained throughout the study period (Table III, Fig. 5).

HDL cholesterol

The mean HDL cholesterol at baseline was 56.78 ± 15.79 mg/dL, with an increase of 1.55 mg/dL observed at the final follow-up (*p*=0.030).

In the subgroup of patients with baseline HDL<40 mg/dL, the mean increased from 34.57±1.99 to 38.29±3.63 mg/dL, corresponding to a rise of 3.72 mg/dL. This difference was statistically significant (*p*=0.023), with a 95% confidence interval for the mean increase ranging from -16.99 to -1.56. In contrast, for patients with baseline HDL >40 mg/dL, the increase was smaller (from 59.72 to 60.98 mg/dL), and not statistically significant (*p*=0.247) (Table III, Fig. 5).

Triglycerides

The mean baseline triglyceride (TG) level among the study participants was 129.46±70.51 mg/dL. At the final follow-up, the mean TG level was 131.35±60.46 mg/dL, representing an

increase of 1.89 mg/dL between the two time points.

In patients with baseline TG levels >150 mg/dL, the mean decreased from 211.07±50.19 mg/dL to 172.33±63.45 mg/dL at the final follow-up. This corresponds to a total reduction of 38.74 mg/dL (p=0.021), with a 95% confidence interval ranging from 6.54 mg/dL to 71.0 mg/dL. In contrast, for patients with baseline TG levels <150 mg/dL, the mean difference between the first and final measurements of 23.99 mg/dL (95% CI: -27.42 to -7.25, p=0.001), although values remained within the normal range (Table III, Fig. 5).

Discussion

During the follow-up period, patients demonstrated a significant improvement in pain as measured by the visual analogue scale (VAS), accompanied by a marked decrease in analgesic use and an increase in physical activity. Although a reduction in weight and BMI was expected as a result of increased physical activity, only a slight, statistically non-significant decrease in both parameters was observed. Nonetheless, it is noteworthy reduction in both parameters was found, without statistical relevance. However, it is noteworthy that patients who received injections over a 24-months period did not experience any increase in weight or BMI.

Regarding laboratory parameters, while the overall average values of all variables showed minimal variation, significant improvements were observed when focusing on patients with abnormal baseline values, particularly in glucose, total cholesterol, HDL, LDL, and TG.

It is important to note that these analytical laboratory values were ordered by patient's primary care physicians or by other specialist outside our rehabilitation service. Although these parameters typically do not fluctuate significantly over six-months intervals, we applied a strict exclusion criterion, omitting patients who lacked these measurements. This reduced our sample size but allowed us to assess not only whether viscossupplementation improved functionality and modifiable CVRF, but also when these effects began to emerge. Examples include the early reduction in analgesic use and the increase in physical activity (Table II), as well as the linear trends observed in lipid profiles (Fig. 5).

Many studies in the literature highlight pain relief as a primary outcome of intra-articular hyaluronic acid (HA) injections (13-15). Acuña *et al*. published a meta-analysis in 2020 evaluating 29 studies and reported an average decrease of 1.87 points in VAS scores following HA injections in patients monitored for up to 12 months (3). In our study, a similar percentage of pain reduction was maintained through 24 months, suggesting that the analgesic effect may extend to improvements in physical activity levels among treated patients. Similarly, Mordin *et al*., in a 2021 systematic review of 215 studies, concluded that intra-articular HA injections can reduce the use of analgesics, NSAIDs, and opioids, while also delaying the need for total knee arthroplasty (13).

Hyaluronic acid viscosupplementation has traditionally been indicated for patients whose response to oral analgesics was inadequate (16). In our study, analgesic consumption clearly decreased following treatment, aligning with findings in the literature and indirectly supporting the analgesic efficacy of HA injections.

It is reasonable to assume that the increase in physical activity observed in this study may be a direct consequence of reduced pain reported by patients. Therapeutic exercise is a fundamental component in the management of hip and knee osteoarthritis, as it helps prevent further cartilage degeneration and improves overall physical conditioning. As pain levels decline, more patients are able to engage in physical activity, and the frequency of such activity also increases, as reflected in our results. In this regard, a 2022 review reported growing evidence on the positive impact of intra-articular injections in hips and knees affected by osteoarthritis, particularly in relation to increased physical activity among patients (17). Given the well-established negative effect of sedentary behavior on CVRFs, it can be hypothesised that pain reduction through viscosupplementation may indirectly improve cardiovascular risk profiles.

Despite the limited number of publications addressing this topic, studies such as the one by Sequi-Domínguez *et al*., which evaluated the effectiveness of physical activity promotion programs in patients with metabolic syndrome, have reported significant improvements in BMI, HbA1c, total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol (18). A similar pattern is observed in our study: increased physical activity, facilitated by pain reduction in patients with symptomatic hip and knee osteoarthritis treated with HA, appears to be associated with improvements in these same parameters. A longitudinal study, published in 2025, aimed to investigate the associations between radiographic damage and serum biomarkers in patients with osteoarthritis over a five-year follow-up period revealed a significant negative association between dyslpidaemia and radiographic progression, although this work was centered in hand osteoarthritis (19).

Although an increase in physical activity was expected to result in a gradual reduction in obesity-related measures, this effect was not evident in the overall average values, nor when analysing the subgroup of participants with a baseline BMI >25. However, it is worth highlighting that, starting from a baseline average in the overweight range, no statistically significant increase in BMI was observed during the study period.

Physical inactivity is a well-known risk factor for cardiovascular disease. Exercise can significantly improve cardiovascular metabolism and function, reduce various risk factors, and help prevent the development of cardiovascular conditions. It also reduces oxidative stress and chronic inflammation, regulates insulin sensitivity and metabolic function, promotes stem cell mobilisation, enhances autophagy and myocardial mitochondrial function, and increases resistance to cardiovascular damage, among other benefits (20).

A similar trend was observed across all laboratory parameters. When analysed globally using total mean values, no statistically significant differences were found between baseline and final assessments. However, when stratifying patients based on pathological baseline

values for each variable (glucose >100 mg/dL, total cholesterol >200 mg/dL, HDL cholesterol <40 mg/dL, LDL cholesterol >110 mg/dL, and triglycerides >150 mg/dL), significant changes were observed in all cases. Specifically, total cholesterol, LDL, and triglyceride levels decreased, while HDL cholesterol increased at the final follow-up compared to baseline. In the case of glucose, a downward trend was noted.

In this study, patients who presented abnormally elevated lipid levels were already receiving specific pharmacological treatment for this condition prior to the injections, and no changes in their therapeutic regimen were detected, apart from viscosupplementation and increased physical activity. Similarly, in patients with elevated fasting glucose levels prior to receiving the hyaluronic acid injection, no therapeutic modifications for their diabetes were made beyond the infiltrations and increased physical activity.

To our knowledge, no studies have directly evaluated the effect of intra-articular HA injections on changes in laboratory markers of cardiovascular risk factors (CVRFs). It is well established, however, that regular physical activity – performed with adequate frequency and intensity – can favourably influence these parameters. Pain from symptomatic knee and hip osteoarthritis often hinders physical activity, severely limiting its benefits in affected patients. Therefore, although modest, our findings support the value of evaluating rehabilitative interventions not only at the joint level but also in terms of their broader systemic impact. The main limitation of this study lies in its retrospective design. Although a large number of patients were initially identified, the final sample was reduced due to strict inclusion criteria requiring the availability of analytical data aligned with control visits and injection schedules.

In conclusion, intra-articular viscosupplementation with HA for symptomatic hip and knee osteoarthritis resulted in pain reduction (as measured by VAS), which in turn allowed patients to reduce sedentary behavior and better manage their weight and BMI. Secondarily, it may have contributed to improvements in CVRF analytical profiles over the medium term in patients with abnormal baseline values.

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