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Intra-Articular Hybrid Hyaluronic Acid Injection Treatment in Overweight Patients with Knee Osteoarthritis: A Single-Center, Open-Label, Prospective Study

Dalila Scaturro [1,*], Fabio Vitagliani [2], Pietro Terrana [3], Daniele Cuntrera [4], Vincenzo Falco [4], Sofia Tomasello [3] and Giulia Letizia Mauro [1]

1 Department of Surgical, Oncological and Stomatological Disciplines, University of Palermo, 90100 Palermo, Italy; giulia.letiziamauro@unipa.it
2 Faculty of Medicine and Surgery, University of Catania, 95100 Catania, Italy; fabiovitagliani93@libero.it
3 Faculty of Medicine and Surgery, University of Palermo, 90100 Palermo, Italy; terranapietro@gmail.com (P.T.); sofia.tomasello@gmail.com (S.T.)
4 Department of Economics and Statistics, University of Palermo, 90100 Palermo, Italy; daniele.cuntrera@unipa.it (D.C.); vincenzo.falco01@unipa.it (V.F.)
* Correspondence: dalila.scaturro@unipa.it; Tel.: +39-3206945411

Abstract: Background: A BMI > 25 is the most decisive, albeit modifiable, risk factor for knee osteoarthritis (KOA). This study aimed at assessing the efficacy of intra-articular injections of hybrid hyaluronic acid (HA) complexes (Sinovial® H-L) for the treatment of KOA in overweight patients in terms of disease severity, cardiocirculatory capacity, and quality of life. Materials: In this single-site, open-label, prospective trial, 37 patients with symptomatic knee OA were assessed at baseline and 3 months after ultrasound-guided intra-articular injection of hybrid HA complexes (Sinovial® H-L). Results: Primary variables displaying a statistically significant improvement after treatment were pain (VAS), disease severity (WOMAC), and cardiopulmonary capacity (6 min walk test). Among secondary variables, quality of life (SF-12) improved significantly, as did analgesic intake for pain control. No statistically significant difference was observed in body fat and muscle mass percentage measured by bioelectrical impedance analysis. Conclusions: Intra-articular hybrid HA injections are significantly effective in improving OA-related disease severity, cardiopulmonary function, and analgesic intake. This supports the role of hybrid HA viscosupplementation as a nonpharmacological treatment to relieve pain, reduce disability, improve quality of life, and limit the risk of polypharmacy in overweight patients with knee OA.

Keywords: knee osteoarthritis; hybrid hyaluronic acid; viscosupplementation; obesity; overweight

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1. Introduction

Knee osteoarthritis (KOA) is a highly prevalent clinical syndrome of joint pain accompanied by a varying degree of functional limitation and decreased quality of life. Among adults aged 60 and older, this chronic musculoskeletal illness is present in 10% of men and 13% of women, or in an estimated 250 million persons worldwide [1]. In terms of pathophysiology, KOA is associated with increased levels of inflammation, and it is characterized by loss of articular cartilage and by subchondral bone changes in terms of turnover, mineralization, and volume [2,3].

Age and sex are two of the main risk factors associated with knee OA, with women more likely to develop OA than men due to differences in knee anatomy and kinematics [4]. Previous knee injuries, joint malalignment and instability resulting in increased mechanical stress, repetitive actions such as kneeling and heavy lifting, and professional sports activities such as long-distance running are all strong risk factors for knee OA [1,3,4]. In this regard, Bullock considers sports accidents an important risk factor for the development of post-osteoarthritis trauma, resulting from an alteration of normal biomechanics resulting

in the impact of dynamic cartilage loads along lines of non-physiological pressure and a higher level of disability [5,6].

However, among the risk factors of KOA, overweight and obesity are the most determinant, although they are considered modifiable. Overweight is defined as the presence of a BMI between 25 and 29.9 kg/m^2. Obesity is defined as the presence of a body mass index (BMI) > 30 kg/m^2, with the degree of obesity defined as class I (BMI 30.00–34.99 kg/m^2), class II (BMI 35.00–39.99 kg/m^2), and class III (BMI $\geq$ 40.00 kg/m^2). The world prevalence of obesity in the last 30 years has increased by 27.5% in adults and 47.1% in children, with a higher prevalence in developed countries in men than women. In Italy, it is estimated that 36.2% of the population is overweight and 10.2% is obese [7,8].

A 2015 meta-analysis showed that being overweight and being obese are significantly associated with higher knee OA risks of 2.45 and 4.55, respectively, and that the risk of knee OA increases by 35% with a five-point increase in BMI [9]. Excess weight correlates with a higher risk of knee OA both by increasing the load on weight-bearing joints and by collating with the inflammatory milieu caused by metabolic syndrome [10].

Treatment objectives for KOA include pain control, reducing stiffness, and improving mobility and quality of life, with avoidance of toxic pharmacological side effects [11].

The guidelines for KOA management suggest conservative treatment as the first approach to the disease. The conservative treatment aims to reduce pain and consists of the single or synergistic use of drugs such as NSAIDs, infiltrations based on corticosteroids or hyaluronic acid, focal muscle vibration (WBV), oxy-ozone therapy (O_2–O_3), platelet-rich plasma injections (PRP), and mesenchymal adipose stem cell (MSC) therapy [12].

Where conservative measures fail, total knee replacement is indicated in patients with severe OA with extensive pain and deformity [13]. Importantly, some studies have suggested that obese patients report worse outcomes and quality of life after surgery, making the need for successful conservative measures all the more pressing [14].

The Osteoarthritis Research Society International (OARSI) periodically updates its guidelines for the nonsurgical management of OA [15]. In its 2019 update, OARSI recommended arthritis education and structured land-based exercise programs, with or without dietary weight management, as the core treatment for KOA.

Recommended pharmacological treatment options include topical nonsteroidal anti-inflammatory drugs (NSAID), cyclo-oxygenase 2 (COX-2) inhibitors, and oral NSAIDs. Notwithstanding, such drugs still bear well-known cardiovascular, gastrointestinal, and renal toxicities; thus, an initial conservative, nonpharmacological approach is to be preferred, especially in the elderly population due to its high risk of polypharmacy.

Intra-articular (IA) corticosteroids and IA hyaluronic acid (HA) were recommended as Level 1B/Level 2 treatments for knee OA, dependent upon comorbidity status, according to the 2019 OARSI guidelines [15]. Viscosupplementation is a nonpharmacological, minimally invasive treatment option for OA. Intra-articular administration of HA-based products was approved in 1997 by the Food Drug Administration (FDA), its aim being to supplement synovial fluid in the affected joint [16]. Intra-articular HA effectively increases viscosity and reduces friction, thus achieving satisfactory pain reduction and improvement in function in OA [17]. HA is furthermore known to mitigate the activity of proinflammatory mediators and to stimulate fibroblast metabolism in animal models, with an analgesic, anti-inflammatory, and chondroprotective effect at the joint level [18]. IBSA Pharmaceutical's Sinovial® H-L Hybrid (Sinovial, IBSA, Lodi, Italy) is a formulation of stable, cooperative hybrid HA complexes produced via a patented thermal process from a combination of high (1100–1400 kDa) and low (80–100 kDa) molecular weight (MW) hyaluronans, without the need for 1,4-butanediol diglycidyl ether (BDDE) or other chemical agents. Sinovial® H-L's unique characteristics include high HA concentration (64 mg in 2 mL), low viscosity with optimal tissue diffusion, and a duration comparable to weakly crosslinked gel.

Previous clinical experiences employing injectable hybrid HA in knee OA showed a statistically significant improvement in pain and function lasting more than 6 months, with no serious adverse events [19–21]. These results were also observed in obese pa-

tients suffering from knee OA, with an improvement in indices such as the International Knee Documentation Committee (IKDC) form, Knee Injury and Osteoarthritis Outcome Score (KOOS), and pain [22]. Such study protocols generally involved two intra-articular injections administered 2 weeks apart. As a rule, the authors advocate for the use of a personalized, patient-guided approach to minimize the number of invasive interventions each patient requires to obtain a comparable analgesic result.

The aim of the study was to assess whether viscosupplementation with Sinovial® H-L positively influenced pain, functionality, and cardiocirculatory capacity in overweight and obese patients, as well as the impact of treatment on quality of life, body mass composition, and need for analgesic treatment.

2. Materials and Methods

This single-site, open-label, prospective trial included 37 individuals, selected between December 2020 and June 2021 among patients treated for symptomatic knee OA at the outpatient rehabilitation clinic of the Paolo Giaccone University Polyclinic in Palermo.

Inclusion criteria were as follows: age > 45 years; BMI > 25 kg/m^2; radiographic evidence of grade I and II knee OA according to the Kellgren–Lawrence classification; no infiltrative treatment in the previous 6 months; written consent for participation in the study.

The exclusion criteria were as follows: concomitant use of anticoagulant and corticosteroid therapy, rheumatological diseases, major hip dysplasia, neurological or vascular diseases, and altered state of consciousness. We also chose to exclude patients with grade III and IV knee osteoarthritis according to the Kellgren–Lawrence classification, as several studies have shown that viscosupplementation performed in the early stages shows a better chondroprotective effect [23,24].

The study was conducted according to the ethical guidelines of the Helsinki declaration; information and data were handled in accordance with the Good Clinical Practice (GCP) guidelines. All participants signed an informed consent form at the time of the enrollment in order to collect clinical data.

Patients were assessed at two timepoints: at baseline (T0) and 3 months after ultrasound-guided intra-articular injection of hybrid HA complexes (T1). As part of the initial assessment (T0), demographic information and clinical data regarding disease state were collected. With regard to clinical data, pain was assessed using the Visual Analog Scale (VAS), quality of life was self-reported via the 12-Item Short-Form Survey (SF-12), and disease severity was evaluated via the Western Ontario and McMaster Universities Arthritis Index (WOMAC) [25]. WOMAC is a 24-item self-administered questionnaire developed for hip and knee OA, assessing the three sub-fields of pain, stiffness, and physical function related to activities of daily living. Patients were furthermore asked to report analgesic intake, expressed as the number of days per week analgesics were required to achieve pain control. Lastly, patients' cardiocirculatory capacity was assessed via a 6 min walk test (6MWT) in terms of distance traveled, and bioelectrical impedance analysis was performed to measure body fat and muscle mass percentages.

Following initial assessment, patients underwent ultrasound (US)-guided intra-articular injection of hybrid HA complexes (Sinovial® H-L) in the knee joint every 15 days. The patient was positioned supine, with the knee slightly flexed or fully extended. With a sterile linear probe and using a transverse approach, the joint was scanned with the US. After lateral subluxation of the patella, a 21 G needle was introduced using a lateral approach, 1–2 cm below the superior lateral margin of the patella. Positioning was verified by aspiration, and then 2 mL of hybrid HA complexes (Sinovial® H-L) were injected into the knee joint, verifying intra-articular positioning in real time via US (direct visualization of viscous fluid or air bubbles). Having removed the needle, knee mobilization in flexion–extension was performed.

Patients were subsequently reassessed after 3 months (T1), and clinical data on disease state post treatment were collected.

To evaluate the effect of HA viscosupplementation in overweight knee OA patients, we assessed the following primary variables for statistically significant differences pre and post treatment:

- pain severity, as assessed by VAS scale;
- disease severity, as assessed by the WOMAC Index;
- cardiocirculatory capacity, as assessed by distance walked in a 6MWT.

Three secondary variables were furthermore considered:

- quality of life, as assessed by SF-12;
- the percentage of fat and muscle mass, measured by bioelectrical impedance analysis;
- analgesic intake (days per week).

Statistical analyses were performed using R software (R Core Team, 2013). Depending on the type of variable, the following statistical tests were performed: *t*-test to compare means for quantitative variables, Mood's median test to compare medians for ordinal variables, and the test for two proportions. For VAS, WOMAC, SF-12, and analgesic intake, data are summarized using median values with their interquartile range (IQR); for all other variables, the mean ± SD was employed. Results were considered statistically significant with a *p*-value (p) < 0.05.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the "Paolo Giaccone University Hospital" in Palermo, Italy (approval number: 11/2020 on 18 December 2020).

3. Results

With regard to demographic data, of the 37 patients, 23 were female (62.2%) and 14 were male (37.8%); patients were aged 45 to 75, with an average age of 63.51 ± 8.15. Of the 37 patients, 16 (43.2%) had a KOA involving the left knee, while 21 (56.8%) had a KOA involving the right knee. The compartment most affected was the medial (78.4%) compared to the lateral (21.6%). In total, 13 (35.1%) had a grade I KOA according to Kellgren–Lawrence classification, while 24 (64.9%) had a grade II KOA. The average BMI of the patients included was 32.08 ± 2.57. Six (16.2%) patients were overweight, while the remaining 31 (83.8%) were obese. Among these, 25 (80.6%) had class I obesity, five (16.1%) had class II obesity, and only one (3.3%) had class III obesity.

Table 1 and Figure 1 show the test results for the three primary variables. A statistically significant (p < 0.01) improvement in cardiocirculatory capacity as measured by distance covered in a 6MWT was observed post treatment, from a mean of 164.3 ± 52.9 m at T0 to a mean of 254.9 ± 52.6 m at T1. A significant reduction (p < 0.01) in disease severity assessed by WOMAC was also observed at T1; median WOMAC was 56 before treatment, plummeting to 26 after viscosupplemention. Thirdly, a reduction in pain severity as assessed via VAS was recorded, from a mean score of 8 at T0 to a mean score of 5 at T1; this was also found to be statistically significant (p < 0.01).

Table 1. Analyses of primary variables.

	T0	T1	*p*-Value
Distance (mean ± SD)	164.3 ± 52.9	254.9 ± 52.6	<0.01
WOMAC (median (IQR))	56 (16)	26 (12)	<0.01
VAS(median (IQR))	8 (1)	5 (1)	<0.01

Legend: T0: baseline timepoint; T1: timepoint 3 months after treatment; SD: standard deviation; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: Visual Analog Scale.

Table 2 shows the test results for the four secondary variables. Quality of life as self-reported via SF-12 displayed a statistically significant improvement (p < 0.05), from a mean of 25 at T0 to a mean of 28 at T1. Regarding the results of bioelectrical impedance analysis, although a mild increase in the percentage of lean mass and a parallel decrease in

fat mass were recorded, they were not found to be statistically significant ($p = 0.62$ and 0.54, respectively). However, a statistically significant difference ($p < 0.01$) was observed in the use of analgesics pre and post treatment. Indeed, before treatment almost half of the patients took analgesics more than twice a week (48.6%), whereas, after HA viscosupplementation, no patients (0%) still required analgesics more than twice a week, and almost half of the patients only took analgesics 1–2 times a week (43.2%). Interestingly, before treatment, 0% of patients took no analgesics, while this percentage rocketed to 56.8% post treatment.

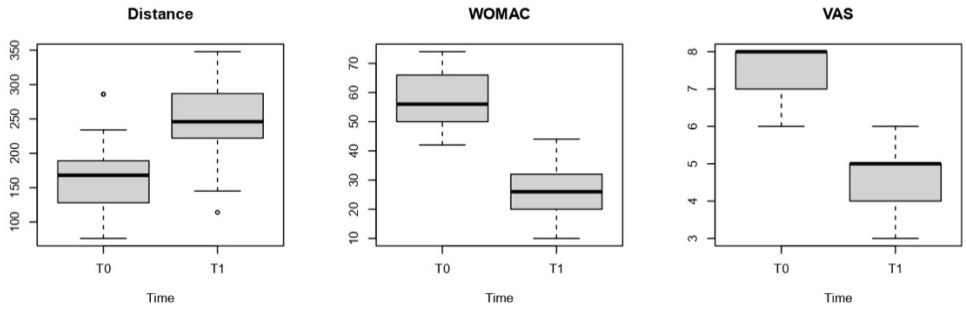

Figure 1. Boxplot analyses of primary variables. Legend: T0: baseline timepoint; T1: timepoint 3 months after treatment; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: Visual Analog Scale.

Table 2. Analyses of secondary variables.

		T0	T1	*p*-Value
SF-12 (median (IQR))		25 (4)	28 (8)	<0.05
Muscle mass (mean ± SD)		36.1 ± 4.5	37.0 ± 3.8	0.62
Fat mass (mean ± SD)		35 ± 3.6	34.5 ± 3.6	0.54
Number of days taking analgesics (median (IQR))	0	0 (0)	21 (56.8)	
	1–2	19 (51.4)	16 (43.2)	
	>2	18 (48.6)	0 (0)	

Legend: T0: baseline timepoint; T1: timepoint 3 months after treatment; IQR: interquartile range; SD: standard deviation; SF-12: 12-Item Short-Form Survey.

Regarding safety, the treatment was well tolerated, and no serious adverse effects were reported by the patients during the study period.

4. Discussion

The authors conducted a prospective trial to investigate the efficacy of HA hybrid Sinovial® H-L viscosupplementation in overweight/obese patients suffering from knee OA. Knee OA is one of the leading causes of disability worldwide and the most common cause of difficulty in walking. This chronic condition has an inestimable impact on quality of life, especially in terms of pain and functional disability [2]. Overweight and obesity are well known to increase the risk of knee OA by mechanical load on weight-bearing joints and by fueling the proinflammatory milieu associated with metabolic syndrome. With advancing age, a proinflammatory picture is established, related to the increase in proinflammatory cytokines and the alteration of protein synthesis. This, especially in obese patients, has a negative impact on skeletal muscle, resulting in muscle weakness and subsequent muscle atrophy [26]. All of this can contribute to the onset of sarcopenic obesity, an increasingly common condition among obese patients, associated with greater difficulty in maintaining body weight, various comorbidities, and a higher risk of mortality [27]. The functional limitation resulting from knee OA is a pejorative factor in such patients' already-limited physical activity level. The latter contributes to the worsening of OA, causing weakness of

the knee extensor muscles, which predisposes to damage to the knee due to less stable and weaker joints [28].

A certainly important role in the prevention and treatment of OA sequelae is played by physical exercise, especially in those patients at high risk of developing OA, such as obese people. A program of physical exercises, based on muscle reinforcement of the quadriceps, muscle stretching, and aerobic activity, is safe and effective in reducing pain and disability related to OA. Physical exercise would appear to play a chondroprotective role as it increases the expression levels of the cartilage synthesis markers, in addition to improving antioxidant defenses and lowering lipid peroxidation levels. However, it is important to consider that excessive or incorrect exercise could adversely affect the course of OA [12].

In patients with KOA, a first approach with conservative treatment is always preferable. For example, intra-articular oxygen–ozone therapy (O_2–O_3) has recently proven effective in patients with KOA in terms of pain reduction and improvement of function and quality of life. Its painkiller action is due to the intrinsic chemical properties of O_3 and its anti-inflammatory activity. O_2–O_3 showed a high safety profile and results almost identical to those of hyaluronic acid in patients with KOA [29].

An additional conservative treatment option for patients with KOA is whole-body vibration (WBV). This type of treatment consists of performing static and dynamic exercises on a vibrating platform, with consequent reinforcement of the quadriceps muscles and improvement of the balance of the patients [30].

Recently, regenerative medicine has found widespread use in the therapy of KOA, with the use of platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs). Their action is related to the inhibition of matrix metalloproteases, inflammatory cytokines (TNF-α and IL-1β), and immune cell maturation, with consequent prevention of cartilage damage and disease progression [31]. Although these treatments are safer and more effective than conventional conservative treatments in terms of pain reduction, functional capacity restoration, and tissue repreparation, the evidence on their efficacy is limited [31].

HA's powerful anti-inflammatory and analgesic potential has proven effective in several disease states including knee OA, in both normal and overweight patients.

Although the intra-articular injection of HA is included in the OA management guidelines, to date, there is conflicting evidence on its effectiveness, especially in the long term, and there is a lack of agreement regarding its use [6]. In clinical practice, there are different types of hyaluronic acid that are not equivalent, whose characteristics depend on the origin, dose, and molecular weight [32].

In recent years, several studies and literature reviews have been carried out to assess the long-term effectiveness of intra-articular AI in KOA, but the evidence is always limited [6,30–33]. Viscosupplementation improves pain, stiffness, and function, in addition to improving the strength of the flexed knee muscles. Unlike intra-articular corticosteroids, intra-articular AI restores the ideal rheological properties of the sinovial fluid, but does not produce an immediate analgesic effect. Some studies agree that the clinical efficacy of intra-articular AI is maintained up to 6 months after treatment before undergoing involution [33].

A control–case study showed a significant improvement in knee pain and function 5 weeks after treatment in patients treated with HA infiltration compared to placebo, with these effects being maintained only up to the 25th week [33]. Sun et al. [34] conducted a study to evaluate the effectiveness of single intra-articular injections of cross-linked hyaluronic acid (HYA-JOINT Plus) compared to the single injections of Synvisc in patients with KOA. Compared to the endpoints examined, the authors noted that the group treated with HYA-JOINT Plus showed significant improvements in pain and stiffness, which remained up to 6 months after the end of treatment. No statistically significant improvement was observed in scores of the WOMAC and Lequesne scale or with respect to the consumption of analgesics. In a retrospective study carried out by Priano et al. [6], it was observed that the administration of two doses of Hymovis at a distance of 1 week

resulted in a reduction in pain both at rest and on the move for about 1 year. This also led to a lower consumption of analgesics (e.g., NSAIDs and paracetamol), emphasizing the importance of treating those patients with K–L stage KOA I who are at risk of pharmacological interference or gastropathy from NSAIDs. Chevalier et al. evaluated the effectiveness of single in-articular injections of HYLAN GF20 compared to placebo in patients with KOA. In addition to reducing the number of intra-articular injections required, the proposed treatment showed efficiency in terms of pain and improved functional mobility for about 26 weeks [32]. A further study showed that repeated intra-articular AI cycles in KOA resulted in greater improvements in pain and functionality compared to a single treatment cycle. The authors also showed a continuous improvement after further treatment cycles up to the fourth treatment cycle, after which a plateau effect was established [35].

The results of our study agree with the literature. In this study, we observed that overweight and obese patients who underwent intra-articular hybrid HA injection experienced a statistically significant five-point reduction in pain severity on the VAS scale. Additionally, a 30-point reduction in disease severity on the WOMAC scale was observed; such a scale includes parameters relative to pain, stiffness, and physical function related to the ability to execute activities of daily living. Our results additionally show a statistically significant three-point increase in quality of life as self-reported via SF-12. Lastly, we observed a reduction in patients' analgesic intake, a particularly crucial endpoint when considering the toxicity burden borne by traditional pharmacological treatment options for knee OA, namely, NSAIDs. Such results, therefore, greatly support the role of hybrid HA viscosupplementation as a nonpharmacological approach to relieve pain, reduce disability, improve quality of life, and limit the risk of polypharmacy in overweight patients.

Individuals affected by OA suffer from more comorbidities and lead a more sedentary lifestyle as compared to healthy peers, and studies have observed a 20% higher age-adjusted mortality in such patients [36]. After viscosupplementation with hybrid HA, we observed a 54.9% improvement in patients' cardiocirculatory capacity as evaluated by 6MWT, supporting a role for such treatment in improving outcomes in overweight and obese patients suffering from knee OA.

Although a non-statistically significant increase in lean mass and a decrease in fat mass were observed post-treatment, significant variations were not to be expected after such a short follow-up period and after only one injection. Furthermore, exercise therapy is a fundamental adjunct in knee OA treatment, and the level of physical activity practiced by patients was not recorded as a therapeutic variable in this study. The authors, however, posit that, by combining a patient-oriented number of sittings with exercise therapy and prolonging observation over a longer follow-up period, the promising results in terms of pain reduction and disease severity will permit improvements in physical function in such overweight patients and, long term, an improvement in lean-to-fat mass percentage ratios.

Limitations of the study include the small number of patients, which is distinctive of small single-center clinical trials, and the absence of a placebo or control group. The latter issue has been addressed in multiple studies and meta-analyses comparing HA with placebo (normal saline) injective treatments, with data proving that HA is superior to saline for the amelioration of symptoms associated with OA, albeit with sometimes contrasting evidence [37–39]. Lastly, a further limitation is the lack of long-term follow-up due to the short observation period of the study. Further studies are, therefore, warranted to assess the superiority of such a treatment in the knee OA population. It may also be useful to compare the effectiveness of repeated cycles of Sinovial H-L hybrid HA against a single cycle of treatment in this category of patients.

5. Conclusions

In conclusion, this study was the first to examine the action and efficacy of Sinovial H-L in an overweight/obese population with KOA. The results shown provide an important addition to most clinical trials to support the analgesic role of hybrid HA in the treatment of knee OA and its already known anti-inflammatory and chondrogenic properties. Crucially,

it also provides precious new data on the safety and efficacy of this noninvasive, nonpharmacological treatment option in overweight and obese patients. Lastly, the US-guided intra-articular injection technique presented above was found to be safe and well-tolerated by patients.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data used to support the findings of this study are available from the corresponding author upon request.

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