HYBRID HYALURONIC ACID VERSUS HIGH MOLECULAR WEIGHT HYALURONIC ACID FOR THE TREATMENT OF OSTEOARTHRITIS IN OBESE PATIENTS

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Osteoarthritis (OA) of the knee is one of the most relevant and debilitating health problems. Obesity represents one of the major risk factor for early development of OA. In the obese population, knee replacement should be delayed and eventually avoided and prefer conservative treatments including intrarticular hyaluronic acid (HA) viscosupplementation. In the present clinical randomized trial, we present a comparison between two groups of 24 obese patients which were randomized to be treated with two intrarticular injections of hybrid (low and high molecular weight) hyaluronic acid (Group A) or two injections of high molecular weight hyaluronic acid (Group B). Patients were followed-up through to 6 months and assessed though IKDC and KOOS scores, pain was evaluated with VAS. All patients reported a significant improvement when compared to baseline value in all outcome measures. At 3-month follow-up, IKDC had significantly improved in patients of Group A, compared to Group B (53.1±1.9 vs 51.4±2.4, p=0.0079) and the same for KOOS (52.1±2.0 vs 50.1±2.9, p=0.010). Furthermore, the difference in KOOS was persistently significant at 6-month follow-up (54.7±2.3 vs 51.7±4.9, p=0.014). The VAS reduced significantly more in Group A at 3 months (3.7±0.5 vs 5.2±0.7, p<0.001). In an obese population, where basal inflammatory pattern increases symptoms of OA and conservative treatment is recommended, HA viscosupplementation improved function and pain of the knee. The treatment with hybrid HA showed better outcomes than high molecular weight HA in obese patients. The combination of the anti-inflammatory action of low molecular weight HA on chondrocytes and the biomechanical role of high molecular weight HA might explain the different results.

Osteoarthritis (OA) is the most common joint disease and one of the most common causes of disability. Indeed, OA represents a painful, debilitating disease that drastically affects quality of life and functional capacity of patients. It is a metabolically active and dynamic process, characterized by the degeneration of cartilage and all joint tissues (1).

Obesity, a rising epidemic and one of the major public health problems, is considered an important independent risk factor in the development of OA (2). It represents a global burden and people affected are constantly increasing worldwide. In a previous report, the World Health Organization (WHO) stated that 500 million of the world's population were obese (3). Both the higher prevalence of obesity and the increasing aging population contribute to make OA a critical problem. The numbers of obese people developing early OA and undergoing total knee replacement (TKR) has consistently been rising (4).

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However, there have been major concerns among surgeons and patients about clinical outcomes and complications of TKR in obese patients, especially due to the morbidities associated such as type 2 diabetes mellitus, hypertension and coronary artery disease, in addition to OA (5) which have detrimental effects on TKR outcomes.

Conservative approaches are core strategies for the management of OA in obese people and these include appropriate disease-related education, lifestyle modification, physical therapist-prescribed exercise programs to address physical impairments and weight loss. Among conservative strategies, intrarticular hyaluronic acid (HA) viscosupplementation is currently widely used in clinical practice, with good results reported in several studies (6, 7). HA is universally accepted as conservative treatment for OA due to its ability to increase the viscoelasticity of synovial fluid toward normal levels, decrease pain, and improve the natural protective functions of synovial fluid in the joint. The high-molecular weight HA (HMWHA) (Sinovial Forte, IBSA) utilized for the present experimentation is composed of a hyaluronan polymer of 800-1.200 kDa (7) and it has been extensively used for clinical experimentation, for the treatment of OA (8-15). The Hybrid Hyaluronic Acid (HHA) (Sinovial HL; IBSA) represents a recent formulation that conjugates a low molecular weight HA (LMWHA, 80-100 kDa) and an HMWHA (1.100-1.400 kDa) obtained through NAHYCO™ technology (16). It has been shown to stimulate extracellular matrix *in vitro* (7), due to the presence of LMWHA and it has proven to significantly reduce the inflammatory process on human primary chondrocytes cultures (17).

In this randomized controlled trial, we evaluated the effects of viscosupplementation with either HMWHA or HHA for the treatment of OA in obese patients.

MATERIALS AND METHODS

This study was performed at the Department of Orthopedic and Trauma Surgery of Campus Bio-Medico University Hospital. The study was conducted in accordance to Helsinki declaration principles and Good Clinical Practice normative.

Inclusions criteria were Body Mass Index (BMI) >30, radiographic evidence of degenerative changes to the knee (stage 3 according to Kellgren-Lawrence radiographic system), symptomatic unilateral pain condition, unresponsive to non-injective conservative therapies (rehabilitation, cryotherapy, rest, NSAIDs). Exclusion criteria were previous surgery on the knee, excessive axial deformity (>5°), knee instability and osteochondral lesion. Hematologic and general health status exclusion criteria were also applied. Since November 2015, 48 obese patients with clinical and radiographic evidence of degenerative changes to the knee were enrolled in the study. Patients were randomized into 2 groups: Group A - 24 patients received 2 injections of HHA (Sinovial HL, 3.2%, 64mg/2ml, 32 mg High-MW 1.100-1.400 kDa+32 mg Low-MW 80-100 kDa; IBSA) and Group B - 24 patients received 2 intra-articular injections of conventional HA (Sinovial Forte, 1.6% 32mg/2ml, MW: 800-1.200 kDa; IBSA)

Clinical assessment

International Knee Documentation Committee (IKDC), Knee injury and Osteoarthritis Outcome Score (KOOS) and Visual Analogue Scale (VAS) were administered to all patients before starting the treatment (baseline), at 3 and 6 months from the end of management. A different and independent investigator, unaware of the previous measurement to ensure a blinded status, recorded each measurement.

Injection procedure

An orthopaedic surgeon in the outpatient clinic injected the product. Knee injection was performed through a lateral approach. The upper pole of dorsal margin of the patella and the femoral condyle were considered as landmarks to identify the point of least resistance. After the sterile dressing of the skin with a 22-G parallel needle to the surface of the bed and tilted toward the articular surface of the patella, operator penetrates through the skin and releases the product after lateral subluxation of patella. Immediately after the injection, the affected knee underwent passive flexion and extension for 3 times, followed by 10 min of resting in supine position.

Statistical analysis

Statistical analyses were blinded. The analyses were

performed using SPSS version 16.0.1 (SPSS Inc., Chicago, Illinois). Primary end-point was the postoperative difference in the IKDC and KOOS scores and VAS scale compared to baseline. Paired *t*-test was used to perform this analysis and unpaired *t*-test to compare the postoperative results between the 2 groups. A P value of 0.05 was set as a threshold for statistical significance. Data were presented with average value and standard deviation (SD).

RESULTS

Demographic and basal characteristics

For the present experimentation, 48 obese patients have been enrolled (BMI 32.6±3.4 Kg/m^2). In the first group (Group A) there were 24 subjects (10 males and 14 females), with a mean age of 61.5 y (range 53-70). In the second group (Group B) there were 24 subjects (11 males and 13 females), with a mean age of 60 y (range 51-69). Baseline evaluation did not find any significant difference between the groups in terms of age, sex and clinical outcomes (IKDC, KOOS and VAS). No patient was lost at follow-up.

Clinical and pain outcomes

In terms of clinical outcomes (IKDC and KOOS), a significant improvement was observed in both groups at each follow-up, when compared to baseline ($p<0.001$). Similarly, VAS improved over time significantly at each follow-up ($p<0.001$). Intergroup analysis showed superiority of the treatment with HHA compared to HMWHA at 3 months in terms of IKDC (53.1±1.9 *vs* 51.4±2.4, p=0.0079) and KOOS (52.1±2.0 vs 50.1±2.9, p=0.010) and the difference in KOOS was also significant at 6-month follow-up (54.7±2.3 *vs* 51.7±4.9, p=0.014). The VAS resulted reduced significantly more in the Group A at 3 months (3.7±0.5 *vs* 5.2±0.7, $p<0.001$) but this difference was not observed at last follow-up (3.0±0.8 *vs* 3.1±0.7, p=0.839). Details of the clinical outcomes are shown in tables I, II and III.

Complications

In Group A, one patient developed aseptic acute arthritis of the knee, while another showed swelling at the site of injection, without any sequelae. In Group B, one patient developed synovitis of the knee and one patient had persistent pain at the site of injection.

DISCUSSION

The authors carried out a prospective controlled trial to investigate the clinical outcomes of HA viscosupplementation with either HHA or HMWHA in an obese population affected by knee OA. According to the results obtained in the present study, both treatments showed to be effective in relieving symptoms. In particular, knee function evaluated through IKDC and KOOS scores significantly improved from baseline in both groups. Furthermore, VAS reduced at each follow-up stage compared to baseline in both groups, thus showing that viscosupplementation can be a beneficial approach in obese patients. However, HHA showed higher effectiveness in terms of pain reduction and function compared to HMWHA. This was evident especially at mid-term follow-up (3 months), with a statistically significant improvement in clinical scores of patients treated with HHA compared to those treated with HMWHA. HHA treatment had better scores also at 6-month follow-up, although this difference is not significant.

Viscosupplementation is considered the main conservative intervention for management of early OA and several HA preparations are nowadays available on market. Its fundamental role is to provide mechanical support to the joint, in order to avoid excessive shear stress on the cartilage. However, FDA approved only a few pharmaceutical preparation of HA, such as Hyalgan®, Supartz®, Orthovisc®, Synvisc® (Hylan G-F 20) and Euflexxa® (18). In the present study, we chose a standard HA, which is widely utilized in clinical practice in Europe. It is composed of a high molecular weight polymer of 800-1.200 kDa. Rheological studies demonstrated that this composite has comparable viscoelastic properties to HHA, since the HMWHA component is similar (7). On the other hand, HHA associates the HMWHA and the LMWHA in its formulation, combined together thanks to NAHYCO™ patented technology; both molecules are not cross-linked and have a respective molecular weight of 1.200±2 kDa and 100±5 kDa. Our group (6) demonstrated that

Table I. *IKDC values over time.*

Follow-up	Group	Average	SD	Intergroup analysis P value
Baseline	HHA	38.8	4.8	0.541
	HMWHA	39.8	5.8	
3 months	HHA	53.1	1.9	0.0079
	HMWHA	51.4	2.4	
6 months	HHA	60.4	2.1	0.075
	HMWHA	57.4	4.8	

Table II. *KOOS values over time.*

Follow-up	Group	Average	SD	Intergroup analysis P value
Baseline	HHA	43.4	4.7	0.907
	HMWHA	43.6	5.5	
3 months	HHA	52.1	2.0	0.010
	HMWHA	50.1	2.9	
6 months	HHA	54.7	2.3	0.014
	HMWHA	51.7	4.9	

Table III. *VAS values over time.*

Follow-up	Group	Average	SD	Intergroup analysis P value
Baseline	HHA	7.6	0.3	0.371
	HMWHA	7.4	0.5	
3 months	HHA	3.7	0.5	<0.0001
	HMWHA	5.2	0,7	
6 months	HHA	3.0	0.8	0.839
	HMWHA	3.1	0.7	

HHA is effective and superior to platelet rich plasma (PRP) in improving clinical outcomes in end career athletes with OA at 1-year follow-up (6). Moreover, *in vitro* studies showed that HHA significantly reduced inflammation biomarkers in a model and human chondrocytes respect to both HMWHA or LMWHA separately considered at transcriptional and protein level (16). In the present study, we showed that significant superiority for all the clinical outcomes assessed was achieved in the group treated with HHA at 3 months follow-up in obese patients affected by knee OA. These outcomes suggest that HHA is a suitable treatment to improve functional outcomes and relieve pain in obese patients.

Better outcomes may be due to the presence of both LMWHA and HMWHA in the same injection. Indeed, next to adequate viscoelastic supplementation (mechanical effect) provided by the HMWHA present in both composites, HHA formulation is efficient in reducing inflammation inside the joint (biological effect) (17) through the LMWHA. *In vitro* studies showed that markers including TNF-α and IL-6 were reduced in primary human chondrocytes cultures (17). Furthermore, it has been reported that LMWHA inhibits prostaglandin E2, nitric oxide and IL-1 having also an antioxidant role, protecting chondrocytes from free oxygen radicals damage (1). Therefore, the therapeutic effectiveness of HHA is based on a strong balance between biomechanical properties of viscosupplementation and biological features that contrast the pathogenic mechanisms of osteoarthritic degeneration of cartilage, chondrocyte damage and inflammatory response.

It is well demonstrated that obese patients represent a critical population, particularly susceptible to articular cartilage damage, increased risk and early development of OA (19, 20) due to the higher mechanical weight but also to the constitutive inflammatory pattern which characterizes obesity (21). Inflammation-induced proteinase and collagenases activity significantly affects matrix contents in structural proteins of the extracellular matrix of joint cartilage (17), thus there is a need of supplementation of such proteins. Chua et al. (22), showed that HA content in synovial fluid of obese patients affected by OA was negatively correlated with medial joint space width and positively correlated with Kellegren-Lawrence radiographic progression of OA (22).

Obesity is, indeed, a predisposing factor for the development of early OA (23) and furthermore it is a factor associated with poor clinical and functional outcomes after surgical management with TKR, yielding also to an increased rate of post-operative complications (23), because of predisposition to cardiovascular events and development of peri-operative infections. Thus, several systemic and local treatments for chondral proteins supplementation have been developed, in order to delay surgical intervention as long as possible and eventually avoid it at all in this critical population. However, there are a few studies concerning specifically obese patients in the literature. A recent study by Nelson et al. investigated the role of oral supplementation of HA and other GAG (Oralvisc®) in obese patients affected by OA, showing that this therapy was safe and effective in terms of pain soothing, systemic inflammation reduction and turnover of the synovial fluid (20). Concerning local injection of HMWHA (1.500-3.600 kDa), it was shown by Eymard et al., that main predictors of failure of injective therapy are the obesity itself and radiologic grade of OA (24).

To our knowledge, this is the first study evaluating HHA in an obese population and is one of the few recent studies that evaluate the treatment of obese population affected by OA. Furthermore, the randomized design avoids allocation bias and confounding factors related to patients' anthropometric and demographic characteristics, which where homogeneous between groups at baseline. However, the paucity of the cohort is the main limitation of the present study, which needs further and larger investigation to find definite scientific significance.

CONCLUSION

In the present clinical randomized trial, we demonstrated that HHA is more effective in soothing pain and improves function in obese patients affected by knee OA compared to HMWHA, especially at

mid-term follow-up. However, further analysis and a longer follow-up are still necessary to assess the best treatment in this challenging population.

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