LIPO-STEM™

ADIPOSE TISSUE MSCs PURIFICATION KIT

ADIPOSE-DERIVED MESENCHYMAL STEM CELLS INJECTION IN KNEE OSTEOARTHRITIS: A CASE REPORT.

Dott. M. Cecchetti, Dott.ssa M. Buoro

bpb medica
www.biopsybell.com

Introduction

Osteoarthritis (OA) is one of the leading causes of disability in the elderly population worldwide[1]. The knee is the most affected joint, with a global prevalence of knee OA of 3.8%, accounting for more than 250 million cases[2-3].

Since replacement surgery can be a premature solution for early knee OA, several conservative treatment approaches have been developed, often by combining several treatment options. These include physical therapy, pharmacologic management (topic or oral NSAIDs, opioids, oral supplements such as vitamin D, collagens, methylsulfonylmethane, curcumin, ginger), intra-articular injections (glucocorticoids, hyaluronic acid, platelet-rich autologous plasma) and minimally invasive surgery (arthroscopic debridement, autologous chondrocyte implantation). Some of these approaches have proven ineffective, others can temporarily reduce symptoms, but have limited or null effects in regenerating cartilage [4-5].

Intra-articular injections of Mesenchymal Stem Cells (MSCs) have been studied in recent years, as a promising therapeutic tool to treat mild to moderate OA. MSCs can differentiate into chondrocytes and secrete bioactive molecules, having anti-inflammatory, lubricating, angiogenic, antiapoptotic, and antifibrotic effects in the receiving site, thus improving symptoms and functional status[4,6].

Adipose tissue is an abundant source of MSCs (Adipose-derived MSCs (ADSCs)), its harvest is easy, inexpensive and fast, can be performed in a single-stage procedure with the following intra-articular injection, and no adverse events have been reported[7,8].

We present a case of knee OA treated with ADSCs processed with a new device: LIPO-STEM™ (Biopsybell S.r.l., Mirandola (MO), Italy).

Patient's history

The patient, an 84-year-old woman with no comorbidities, had suffered progressive left knee pain for about 2 years, increasing when flexing the knee in common daily activities, such as walking, climbing stairs or rising from sitting. Conservative therapy (oral NSAIDs, Hyaluronic intra-articular injections) had previously failed, partially reducing the pain for just a few weeks.

Physical examination revealed articular effusion, limited and painful mobility and articular crepitation. X-ray *(fig. 1)* and Magnetic Resonance Imaging *(fig. 2)* showed a moderate knee OA (chondropathy, osteophytes, reduction of the femorotibial space, a torn medial meniscus and a moderate effusion).

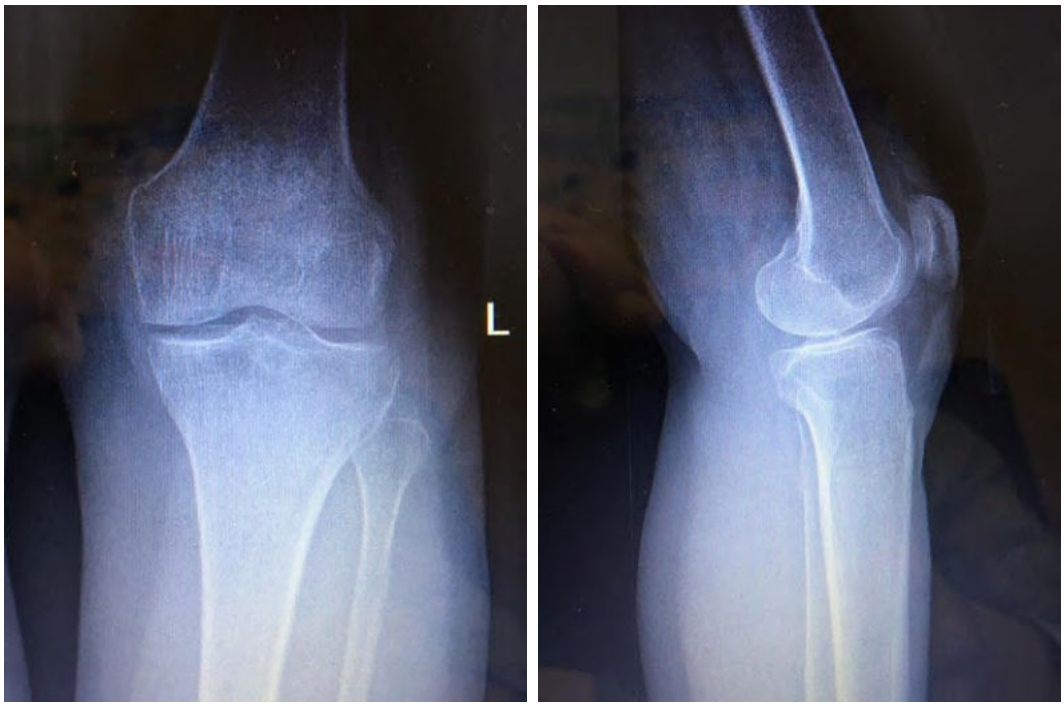


Figure 1. Pre-operative X-Ray of patient's left knee.

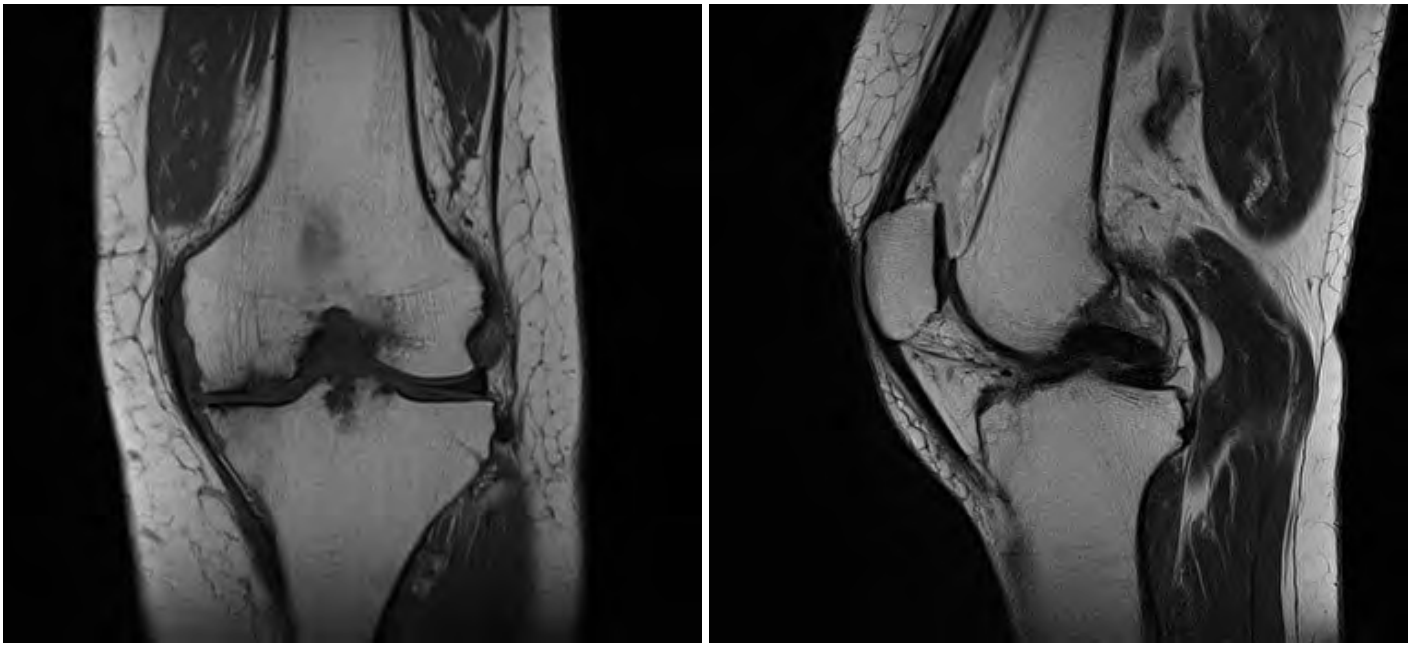


Figure 2. Pre-operative MRI image of patient's left knee.

Material and methods

Given the patient's age and the moderate severity of OA, surgery was excluded and we decided to perform a minimally invasive therapy: intra-articular injection of ADSCs processed with LIPO-STEM™ (Biopsybell S.r.l., Mirandola (MO), Italy).

This is a single-use kit intended for aspiration, processing and grafting of autologous adipose tissue, packed in a sterilized box containing all the components needed for the procedure. The kit *(fig. 3)* includes different sizes of syringes for adipose tissue Klein solution infiltration, adipose tissue liposuction and fat injection, metal blunt cannulas for adipose tissue Klein solution infiltration (16 G Ø) and lipoaspiration (13 G Ø), a 16 G grafting needle, a filter bag for adipose tissue microfragmenting and washing, a drip chamber with a tip to perforate the bag of saline solution with clamp, a waste collection bag.

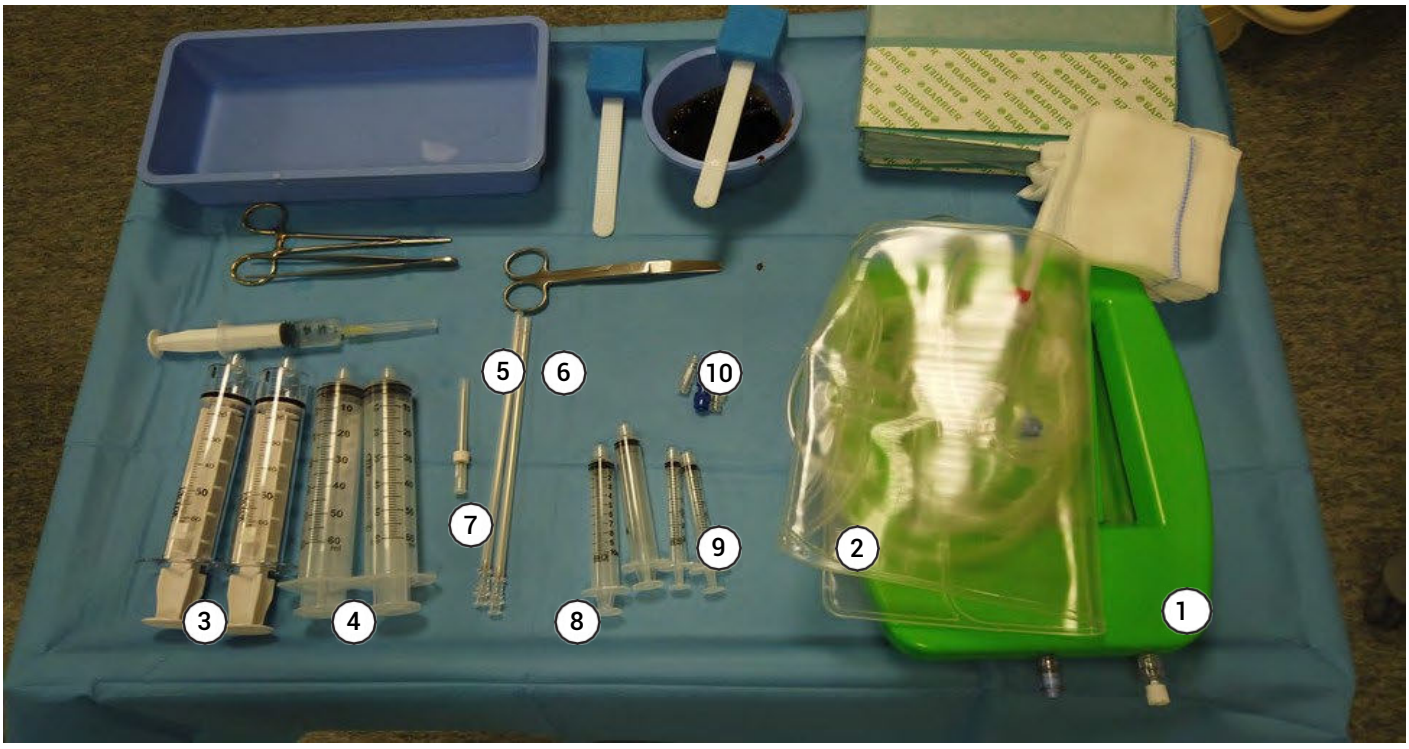


Figure 3. Surgery kit: LIPO-STEM™ kit, local anaesthetic syringe, Klein solution bowl, ancillary surgical instruments.

STANDARD KIT COMPOSITION:

1. LIPO-STEM™ system with filtering bag
2. Waste bag and Infusion with clamp
3. VacLok syringes 60ml
4. Syringes 60ml
5. Klein cannula 16G
6. Lipo-aspiration cannula 13G
7. Infiltration needle 16G x 50mm
8. Syringes 10ml
9. Syringes 3ml
10. Combi caps LLF/LLM and Luer connectors LLF/LLF

In the operating room, the patient was placed in the supine position and antibiotic prophylaxis was intravenously administered (Ceftriaxone 1g). After scrubbing with an iodopovidone-based solution and draping, the abdomen was chosen as the donor site for the adipose tissue.

Figure 4. Klein solution infiltration in the subcutaneous abdominal tissue.

Through a 2-3 mm cutaneous incision made under local anaesthesia (1 cc of a 2% Lidocaine), the subcutaneous abdominal tissue was infiltrated with 150 ml of Klein solution *(fig. 4):*

- 20 ml of 2% lidocaine
- 0.25 cc of 1 mg/ml adrenaline
- 2 cc of sodium bicarbonate
- 250 ml of 0.9% saline solution

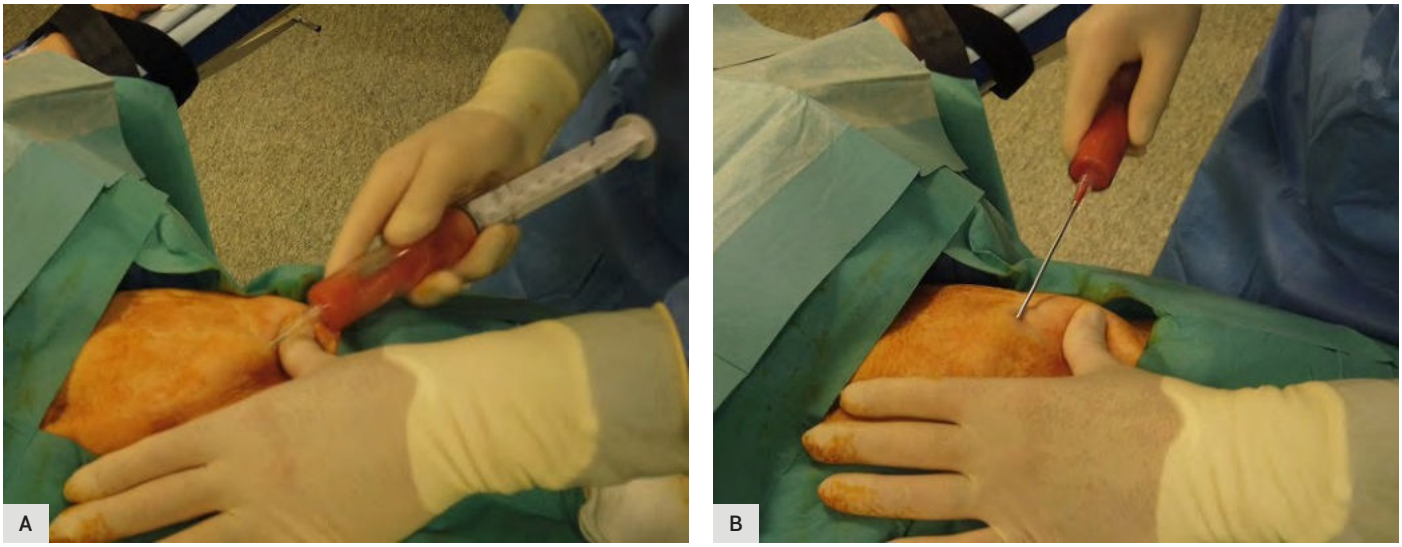


Figure 5. Lipoaspiration in the previously infiltrated area.

After 7-10 minutes, about 30 cc of adipose tissue were harvested through a wet liposuction technique *(fig. 5-6)*. The abdominal incision was closed with a thin bandage, and an adhesive foam pad was applied to the treated area.

Figure 6. Harvested adipose tissue before the microfragmentation and purification process.

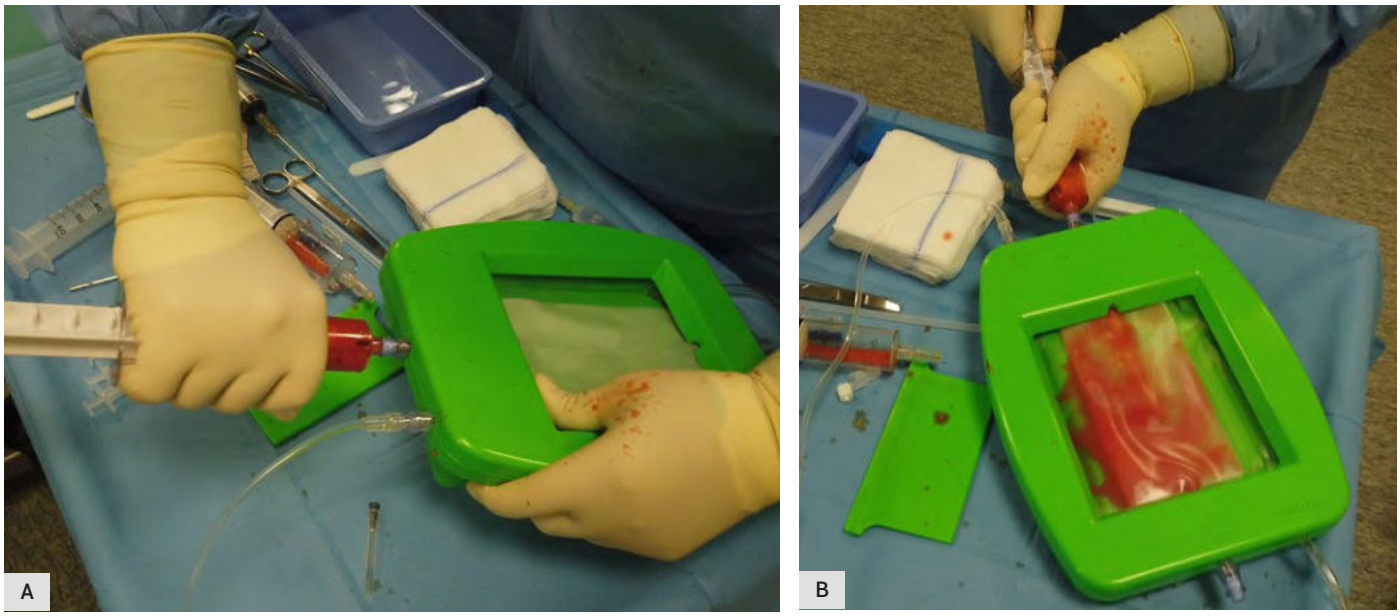


Figure 7. Lipoaspiration syringe connection to the device's LIPO-IN valve (A) and transfer into the LIPO-STEM™ processing bag.

The collected tissue was immediately processed with the LIPO-STEM™ device. The liposuction syringe was connected to the device's LIPO-IN valve *(fig. 7A)* and the adipose tissue was transferred to the filter bag *(fig. 7B)*.

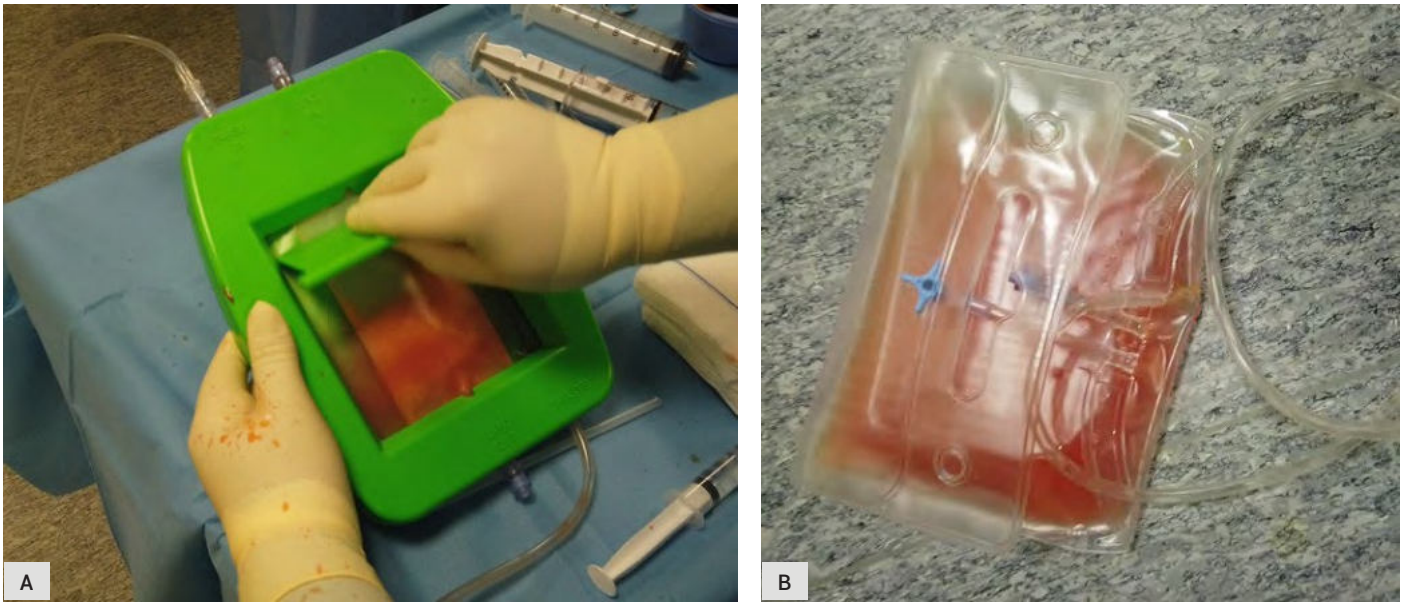


Figure 8. Adipose tissue processing phase: microfragmentation and purification (A) from all pro-inflammatory residues, which are discharged in the waste bag (B).

Following the manufacturer's instruction, the tissue underwent a delicate and fast mechanical processing in a continuous saline solution washing *(fig. 8-A)*: the clusters of adipose tissue were reduced in size, while the blood components with pro-inflammatory properties and the oily substances were washed away and eliminated through the waste bag connected to the bottom of the filtering box *(fig. 8-B)*.

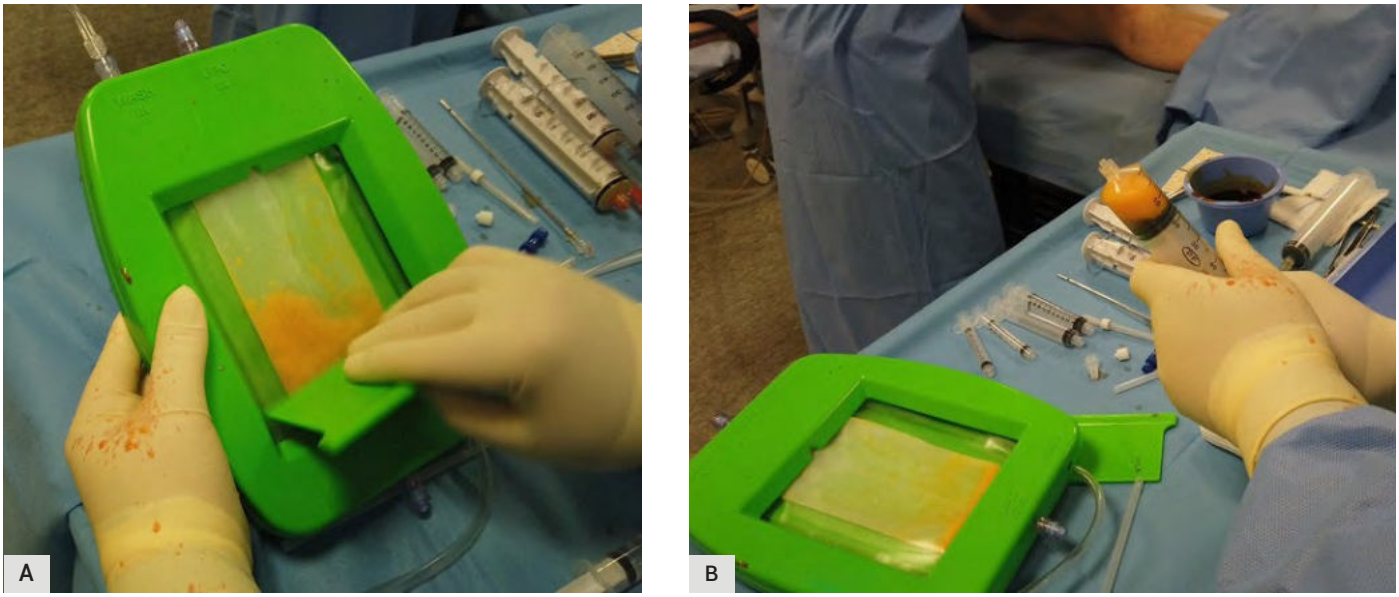


Figure 9. Adipose tissue processing phase: the resulting product.

In about 5 minutes, we obtained 7 cc of microfragmented micronized adipose tissue product *(fig. 9)*, which was injected intra-articularly in the left knee *(fig. 10)*, kept in flexion position, after cutaneous infiltration with 1 cc of 2% lidocaine, through lateral access. The injection point was medicated with a sterile dressing.

Figure 10. Processed adipose tissue intra-articular reinjection in the left knee.

Results

The procedure was painless, just a mild and brief discomfort was perceived by the patient during the intra-articular injection, and she referred the knee pain totally ceased immediately after the injection. The articular crepitation when flexing the knee was no longer detectable as well. The patient was discharged 30 minutes after the procedure with paracetamol 1000 mg if needed, and with the indication to avoid efforts, but with permission to weight-bearing.

The postoperative course was uneventful and the patient was very satisfied with being able to return to her normal life soon after.

Outpatient controls were made at 1,3 and 6 months postoperatively. In this timeframe physical examination was unremarkable and the patient referred an almost complete resolution of the algic symptoms, with no need for any further pharmacological or physical therapy.

Discussion

Knee OA is a chronic inflammatory disease responsible for an increasing number of disabilities and social costs worldwide[1-3]. Since surgery does not always reduce the pain and is recommended only in severe cases, a lot of different conservative therapies have been developed over time, aiming at reducing the symptoms and delaying disease progression[9]. Among these treatments, the intra-articular injection of MSCs is gaining increasing attention[10].

MSCs are multipotent cells with the ability to differentiate into various tissues (bone, tendon, articular cartilage), and have trophic, anti-scarring, immunomodulatory, mitogenic, anti-apoptotic and anti-microbial properties, due to their production of growth factors, bioactive elements and cytokines that detect and signal changes in the microenvironment where they reside[11]. Perivascular cells or pericytes have been reported as the progenitors of MSCs[12]. Pericytes and MSCs can be found in the extracellular matrix of various tissues, mainly the bone marrow and, more abundantly, in the adipose tissue. This is an ideal donor site because of its easier access, a much-reduced donor site morbidity, and its richness of vascular niches, thus representing an important source of potential healing and regenerative pericytes and ADSCs[13].

Intra-articular injections of autologous fat tissue in patients with knee OA have shown promising results in several studies[10], providing volume, cushioning, support, potential healing and regenerative capabilities[14]. A recent systematic review has shown higher clinical and imaging scores in patients treated with ADSCs, with clinical improvement maintained for up to 1 year and evidence of regenerated hyaline cartilage[13]. However, studies on MSCs intra-articular injection are heterogeneous and standardized protocols for tissue collection and processing are lacking[10].

LIPO-STEM™ is a new device that allows the processing adipose tissue from normal liposuction and obtaining a micro-fragmented, micronized product, ready for autologous injection in the affected joints in one operating stage, with no need for laboratory manipulation (enzymatic processing, haemolysis, culturing), thus greatly reducing the preparation time and avoiding higher costs, ethical issues and regulatory constraints.

Fat tissue can be easily and rapidly harvested from the abdomen or hip/thigh regions, with minimal donor-site morbidity. While the donor region is being dressed, the lipoaspirate undergoes a rapid, delicate and easy mechanical processing and is reduced in size through a system of filters and a continuous saline solution washing that eliminates blood residues with pro-inflammatory properties, and the final product is ready to be injected immediately.

In our case, both the liposuction and the intra-articular injection were performed under local anaesthesia in less than 1 hour, the patient reported just a little discomfort during the injection, but she had instant pain relief in her knee and she was able to go home with no contraindications to weight-bearing. No adverse events were observed, and the patient was very satisfied with the significant and prolonged improvement in pain control, functional status and quality of life, with no need for pharmacological therapy up to 6 months post-treatment.

Conclusions

Although literature lacks well-designed and comparative standardized studies, autologous micronized fat injections represent a promising treatment option in OA. Albeit this is a single case report, part of a larger ongoing study, the results are very encouraging and LIPO-STEM™ appears to be a very handful, safe and effective device for the conservative treatment of mild to moderate OA or in patients not responsive to other current treatments.

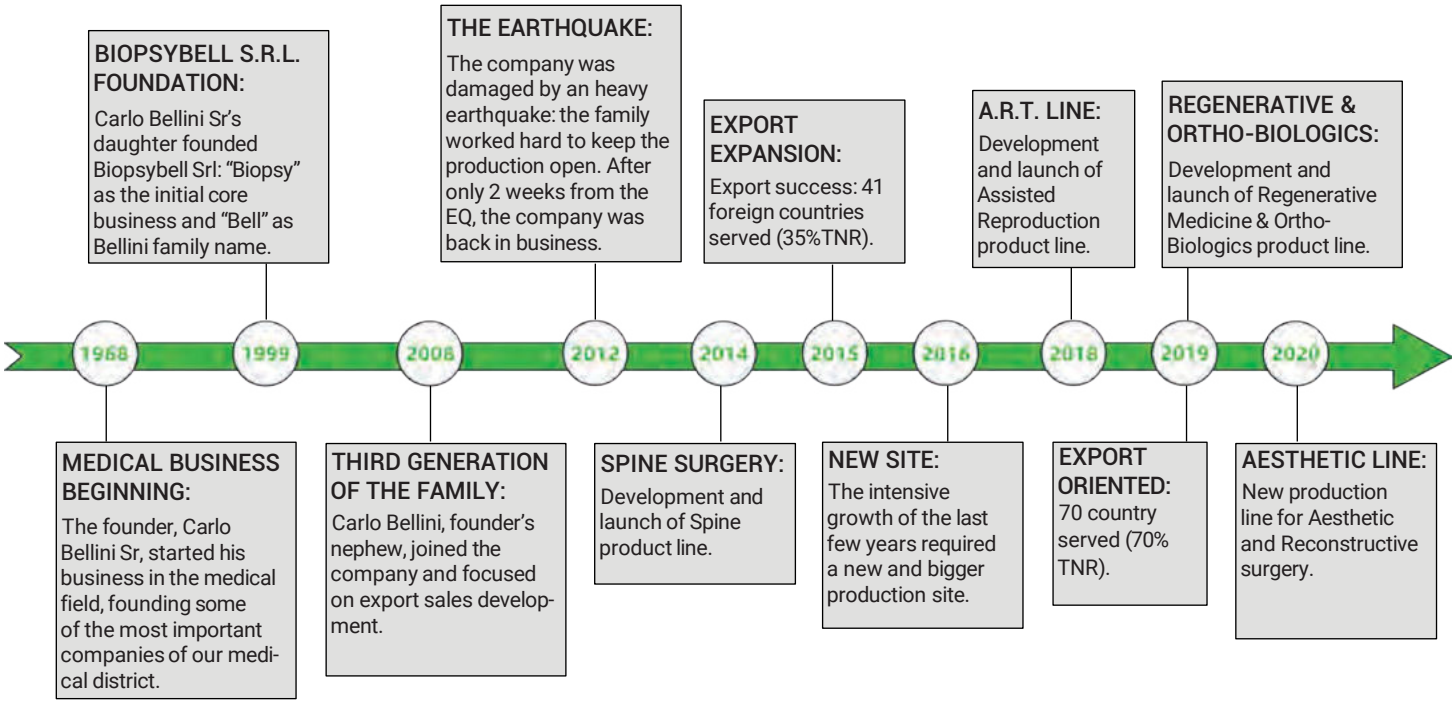
REFERENCES

1. *Panchal J, Malanga G, Sheinkop M. Safety and Efficacy of Percutaneous Injection of Lipogems Micro-Fractured Adipose Tissue for Osteoarthritic Knees. Am J Orthop 2018;47(11):1-11.*
2. *Dall'Oca C, Breda S, Elena N, et al. Mesenchymal Stem Cells injection in hip osteoarthritis: preliminary results. Acta Biomed 2019; Vol. 90, Supplement 1: 75-80.*
3. *Cross M, Smith E, Hoy D et al. (2014) The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 73:1323–1330.*
4. *Fuggle NR, Cooper C, Oreffo ROC, et al. Aging Clinical and Experimental Research (2020) 32:547–560.*
5. *Schiavone Panni A, Vasso M, Barile A, et al. Preliminary results of autologous adipose-derived stem cells in early knee osteoarthritis: identification of a subpopulation with greater response. International Orthopaedics (2019) 43:7–13.*
6. *Striano R, Chen H, Bilbool N, et al. Non-Responsive Knee Pain with Osteoarthritis and Concurrent Meniscal Disease Treated With Autologous Micro-Fragmented Adipose Tissue Under Continuous Ultrasound Guidance. CellR4 2015; 3 (5): e1690.*
7. *Damia E, Chicharro D, Lopez S, et al. Adipose-Derived Mesenchymal Stem Cells: Are They a Good Therapeutic Strategy for Osteoarthritis? Int J Mol Sci. 2018 Jun 30;19(7).*
8. *Cattaneo G, De Caro A, Napoli F, Chiapale D, Trada P, Camera A. Micro-fragmented adipose tissue injection associated with arthroscopic procedures in patients with symptomatic knee osteoarthritis. BMC Musculoskelet Disord. 2018 May 30;19(1):176.*
9. *Perdisa F, Gostyńska N, Roffi A, Filardo G, Marcacci M, Kon E. Adipose-Derived Mesenchymal Stem Cells for the Treatment of Articular Cartilage: A Systematic Review on Preclinical and Clinical Evidence. Stem Cells Int. 2015; 2015:597652.*
10. *Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). 2020 Feb;72(2):149-162.*
11. *Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell 2011; 9: 11-15.*
12. *Crisan M, Yap S, Casteilla L, Chen C-W, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem cell 2008; 3: 301-313.*
13. *Usuelli FG, D'Ambrosi R, Maccario C, et al. Adipose-derived stem cells in orthopaedic pathologies. Br Med Bull. 2017 Dec 1;124(1):31-54.*
14. *Di Marino AM, Caplan AI, Bonfield TL. Mesenchymal stem cells in tissue repair. Front Immun 2013;4:201.*

OUR COMPANY

BPB MEDICA™ is an Italian manufacturing company specializing in the design, production and marketing of high-quality healthcare products for medical use and medical-surgery devices.

BPB MEDICA™ was founded in 1999 by the Bellini family, boasting thirty year's experience in the biomedical sector. The founder, Carlo Bellini Sr., started the business in 1968 and has passed down ethics, integrity and spirit of sacrifice to his heirs. Today BPB MEDICA™ has leveraged its 50 years of experience to develop new innovative product lines, growing the company on an international level.



BPB MEDICA™'s philosophy is to grow alongside the needs of patients, doctors and hospital staff in general. Backed by the experience acquired by the company's specialized technical personnel and thanks to newly-adopted technologies, BPB MEDICA™ has quickly managed to make a name for itself in the domestic and international markets.

OUR NUMBERS

50 YEARS
EXPERIENCE

70
COUNTRIES SERVED

500
CUSTOMERS

10.000.000
PROCEDURES
perfomed with our devices

OUR PRODUCT LINES

- SPINE SURGERY
- ORTHO-BIOLOGICS
- ASSISTED REPRODUCTION
- BIOPSY
- INTENSIVE CARE
- AESTHETIC

BPB MEDICA™ provides painstaking service to its clientele and its primary aim is product quality. Our **internal Regulatory and Quality Departments** offer full-service support to our customers in the following activities:

- Quality Systems
- Regulatory Affairs
- Technical documents preparation
- Clinical experimentation
- Vigilance
- Formation
- OEM and Private Lable regulatory and quality support

Our **Quality Department** conducts rigorous tests, from the raw materials to the equipment and the finished product. This allowed the company to obtain CE, ISO 13485 and the establishment registration by FDA.

Thanks to the **internal R&D Department** BPB MEDICA™ conducts constant research on the reference pathologies with an aim to ever-better qualifying, improve its production standards and aid the development of new products. Functional tests are performed by **R&D Department** in concert with Quality Department to demonstrate the product performance and to make sure that new products maintain their functional characteristics even in the worst case.

BPB MEDICA™ is an established and experienced contract medical equipment manufacturer, with:

- Advanced ISO 8 cleanroom facility for manual & automatic assembly and packaging.
- Metal refinishing department for cutting, grinding, sharpening, cleaning, echogenic marking, sealing, reduction
- Moulding department with vertical and horizontal moulding machines.
- Computerised warehouse with top-selling items always available in stock ready to be shipped within 24 hours.

OUR SERVICES

QUALITY & REGULATORY DEP.
Our primary aim is product quality and to provide painstaking service. Our regulatory and quality teams conduct rigorous tests for this purpose.

OEM & PRIVATE LABEL SERVICES
À la carte production, with customer's brand name and custom colour. Full-service support of Regulatory and Quality documentation.

RESEARCH & DEVELOPMENT
Constant research to increase production and quality standards while developing new products.

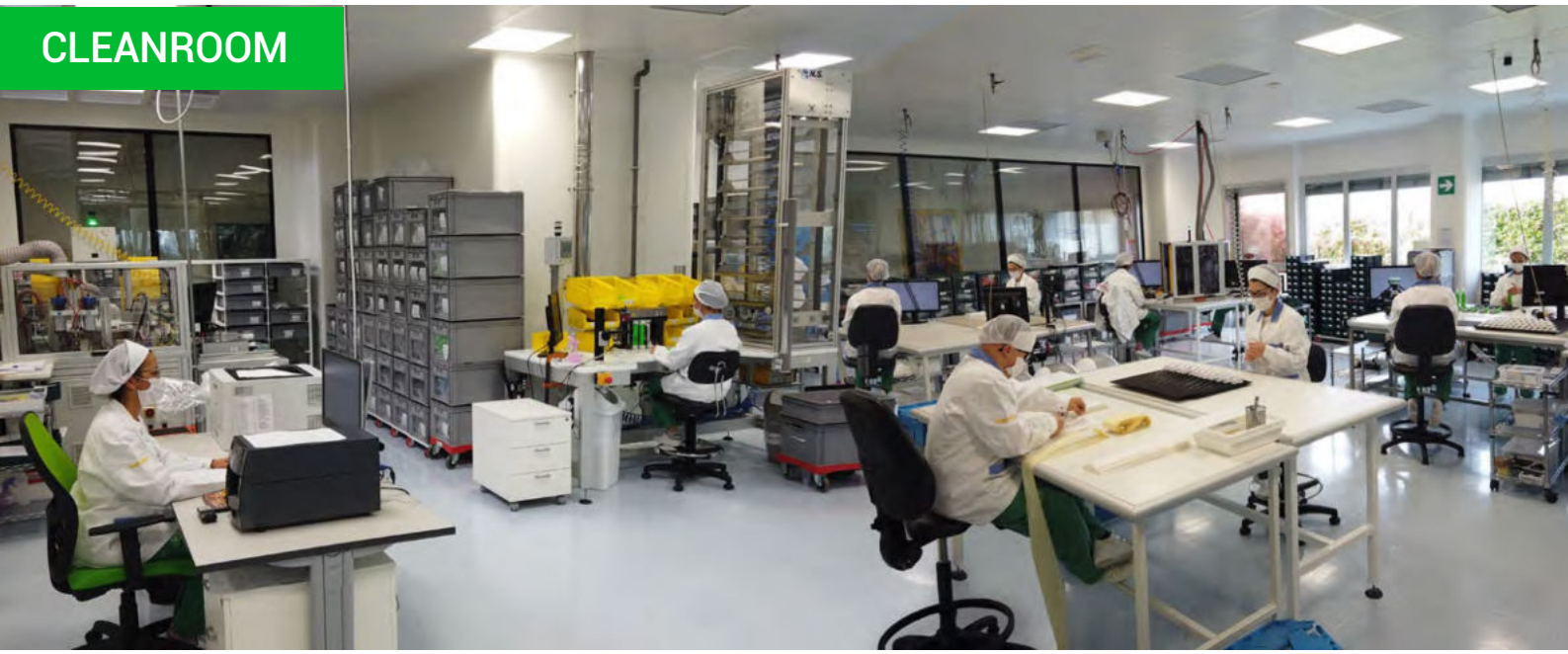
MARKETING SUPPORT
Video tutorial, case report, presence at the major medical congresses, organization of training and courses.

PRODUCTION PROCESS CONTROL
Complete manufacturing process carried out internally, from design to final packaging.

FOUR WEEKS DELIVERY
Thanks to the optimization of the production process, we satisfy our customers' orders within 4 weeks.

CUTTING, GRINDING & ELECTROPOLISHING

CLEANROOM



MOULDING DEPARTMENT

Contact us for further information:

BIOPSYBELL S.R.L.
Via Aldo Manuzio 24
41037 Mirandola – MO – ITALY
T. +39 0535 27850 – F. +39 0535 33526
C.F./P.Iva 02615000367

BPB MEDICA™
www.biopsybell.com
international1@biopsybell.it

SCRLPKV00EN - Rev.01 19/05/2022