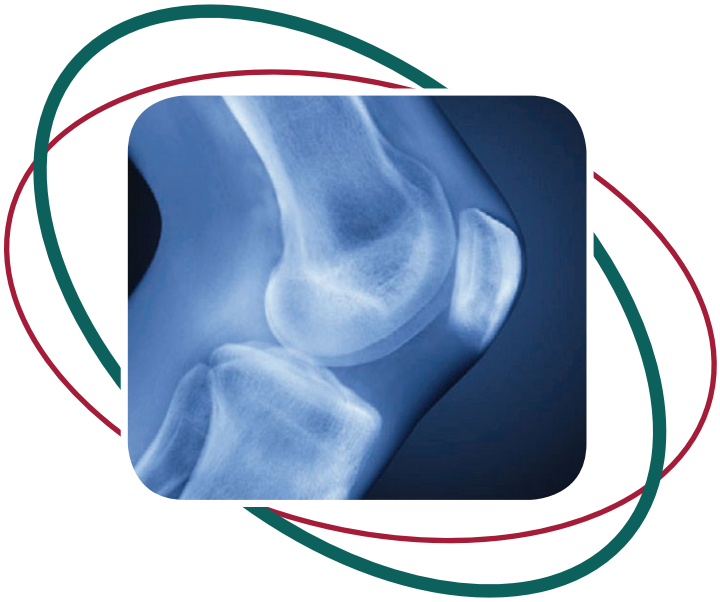
Providing medical service using stromal vascular fraction cells isolated from adipose tissue

Cellthera, Ltd.

Let your cells heal your body



Version 2.1

About Cellthera, Ltd.

Cellthera, Ltd. was founded in 2010 as a biotech company with a vision of bringing its own original scientific findings in the field of the stem cell technology into clinical practice. After 10 years of experience in stem cell-based research we optimized our own technology for the isolation of adult stem cells from adipose tissue. To date (December 2013) we have treated 1856 joints in 1128 patients suffering from osteoarthritis creating the largest dataset worldwide.

In 2011, Cellthera, Ltd. became a member of the International Consortium for Cell Therapy and Immunotherapy (ICCTI; www.iccti.eu) that brings together internationally recognized scientists, physicians and bioengineers from more than 30 countries worldwide. In 2013, State Institute for Drug Control of the Czech Republic approved Cellthera, Ltd. as a tissue bank. Currently we are promoting our ideas into markets in Europe, Asia and North America.

We are committed to providing you with a novel, effective and safe cell technology to improve quality of life for your patients.

Jaroslav Michalek, MD PhD
Cellthera founder & CEO

Osteoarthritis

Osteoarthritis (OA) is a disease of „wear and tear" leading to structural and functional cartilage damage of the weight-bearing joints, such as the knees, hips or spine. It also occurs in the finger joints, neck and the big toe.

OA is the most common type of arthritis, affecting more than 50% of population aged 50 years and over.

It is possible to prevent OA by optimizing exercise (walking, bicycling, swimming) and body weight.

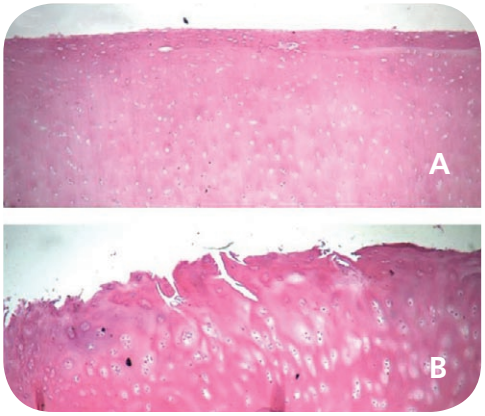


Figure 1
Comparison of healthy (A) and arthritic (B) cartilage containing vertical fissures caused by collagen degradation. Figure was adopted from The Department of Cell Biology at Yale Medical School, *www.med.nyu.edu/medicine/labs/abramsonlab/*

Common symptoms:

- **joint pain or soreness in joints when moving;**
- **discomfort or joint stiffness after long period of inactivity;**
- **inflammation.**

Standard therapeutic options:

- **physical therapy;**
- **supportive devices;**
- **painkillers;**
- **chondroprotectives (e.g. chondroitin, glucosamine);**
- **steroids, hyaluronic acid intraarticularly;**
- **platelet-rich plasma intraarticularly;**
- **surgery – total joint arthroplasty.**

Complications in Standard Therapy

Total knee and hip arthroplasty *	
Procedure-specific complications	**Long-term complications**
Dislocation of the joint	Intraoperative periprosthetic fractures (~1%); fractures of femur and pelvis
Infection (1-2.5%)	Late-onset infections (1-2%)
Blood loss; early hemorrhage	Osteolysis (1-10%)
Adverse reactions to an anesthesia or medications	Excessive bone formation around the implant
Cardiovascular, respiratory or renal failure; electrolyte imbalance	Change in the leg length
Temporary or permanent nerve damage	Use of mobility aids, e.g. canes, crutches and walkers
Wound breakdown; nonunion, a failure of the bone healing process	Loosening of the prostheses (1.4-3.2%)
Deep venous thrombosis (1-2.6%); blood clots in the legs, pelvis, or lungs	Premature wear-out of the implant or failure of the components
Increased mortal risk 30 and 90 days after surgery	
Stroke	
Heart attack	
Persistent pain	

** Schmarzried, J Bone Joint Surg Am 1999; Lassen, N Engl J Med 2008; Thorey, Technol Health Care 2008; Schrama, Arthritis Care Res 2010; Bistolfi, Orthop Traumatol 2011; Kalore, Open Orthop J 2011; Lygre, Acta Orthop 2011; Parry, J Bone Joint Surg Am 2011; www.medicinenet.com*

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Cell Therapy and Cellthera Case Control Study

In 2010-2013, Cellthera performed in collaboration with the International Consortium for Cell Therapy and Immunotherapy (www.iccti.eu) a case control study in OA patients using original cell-based technology. It relies on adipose tissue collection by tumescent liposuction followed by stromal vascular fraction (SVF) cells isolation. SVF (see Fig. 2) isolated from adipose tissue contains about 1000 times larger amount of mesenchymal stem cells in comparison to the same volume of bone marrow. SVF includes regenerative cells such as endothelial precursors, pericytes, regulatory T cells and macrophages. SVF cells serve as an excellent source of autologous adult non-manipulated stem cells with self-renewal potential.

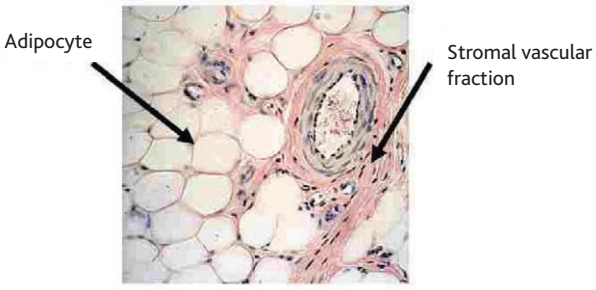
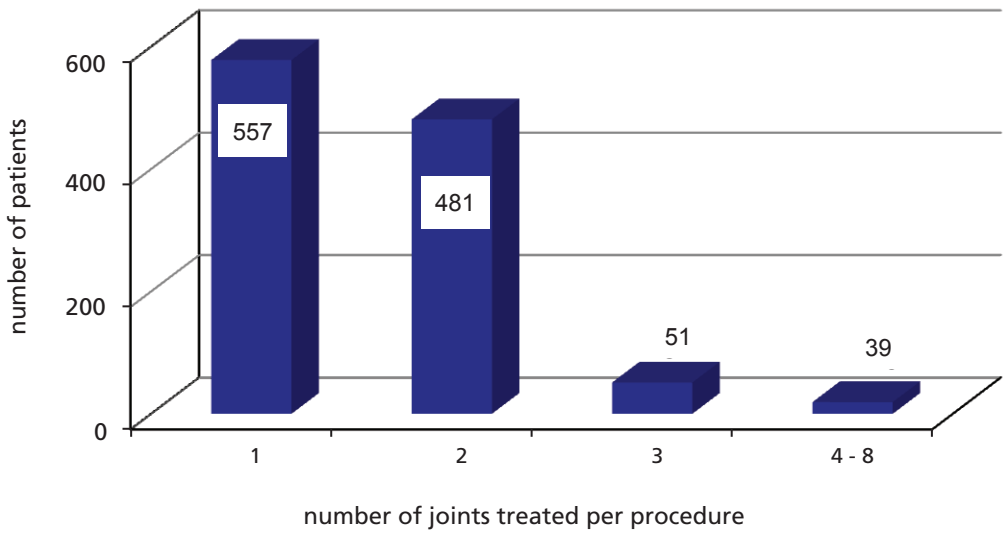


Figure 2
Localization of stromal vascular fraction (SVF) surrounding small vessels of the adipose tissue

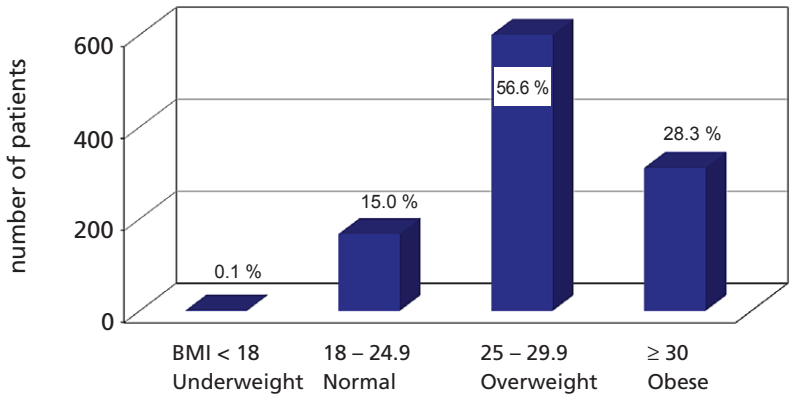
In the case control study, we treated a total of 1856 joints in 1128 patients with grade II-IV knee and hip OA (53% males, 47% females). SVF cell processing was performed by Cellthera-certified technician. Patients were followed for 12.1-54.3 months (median 17.2 months) by a certified orthopedic surgeon or traumatologist in 7 clinical centers. Clinical status of patients was evaluated at different timepoints by a certified physician and it included pain evaluation, analgesic drugs usage, grade of limping, stiffness and extent of joint movement.

Number of joints treated in patients with OA

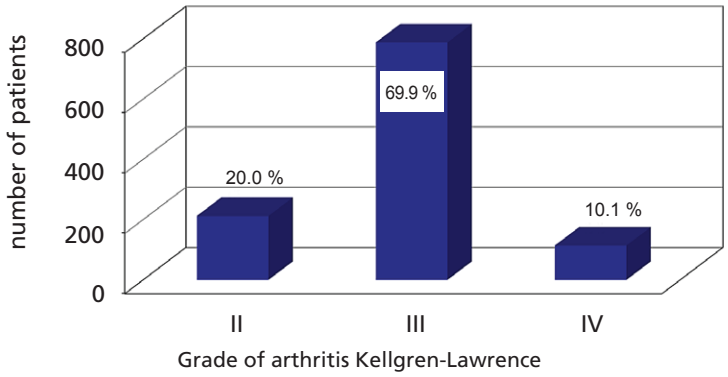


Patient Characteristics

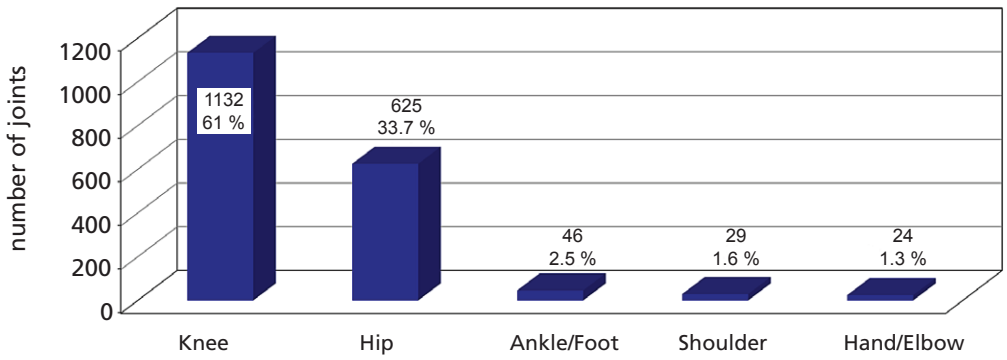
Body mass index



Osteoarthritis severity



Joints treated by location



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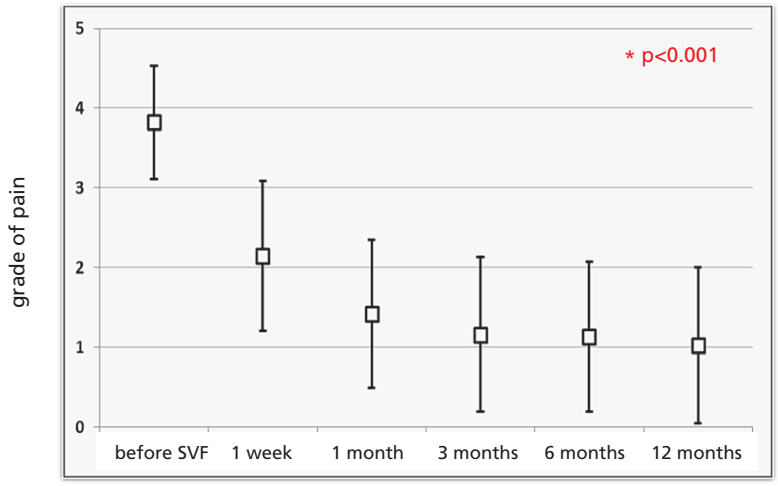
Cellthera and ICCTI Study Results

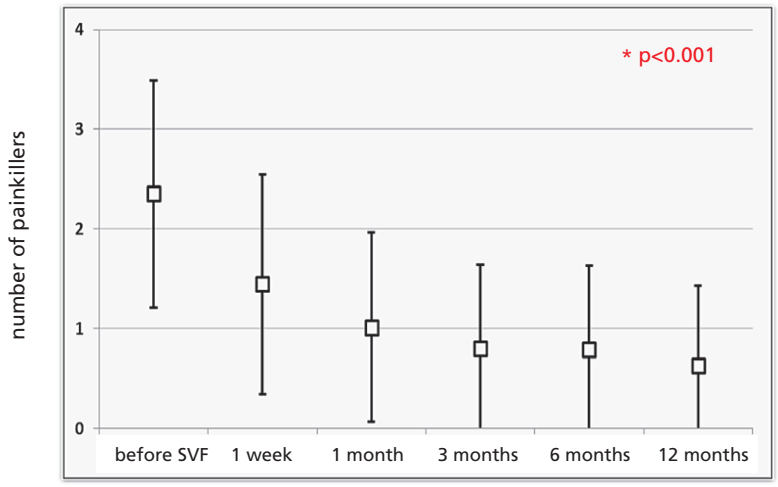
Semiquantitative pain evaluation



Grade of pain

0 no pain
1 minor not frequent pain
2 minor frequent pain
3 moderate pain
4 severe pain
5 unbearable pain requiring daily use of painkillers

Analgesic drugs per week



Number of painkillers

0 no painkillers
1 1-5 painkiller tablets/cream per week
2 6-15 painkiller tablets/cream per week
3 16-25 painkiller tablets/cream per week
4 more than 25 painkiller tablets/cream per week

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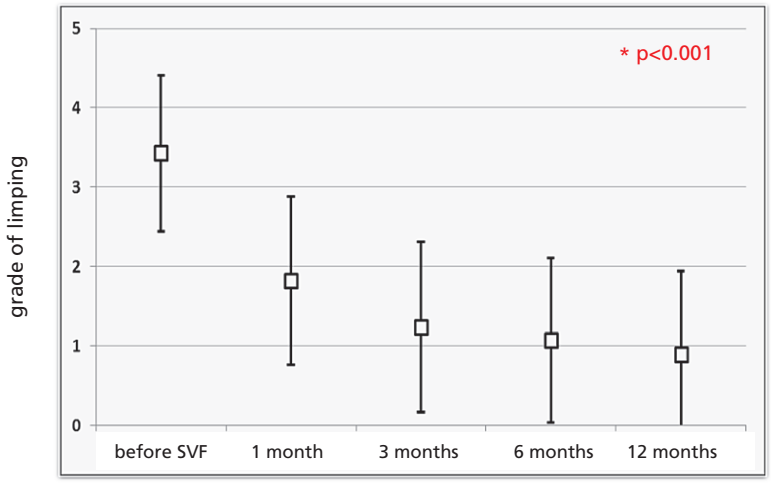
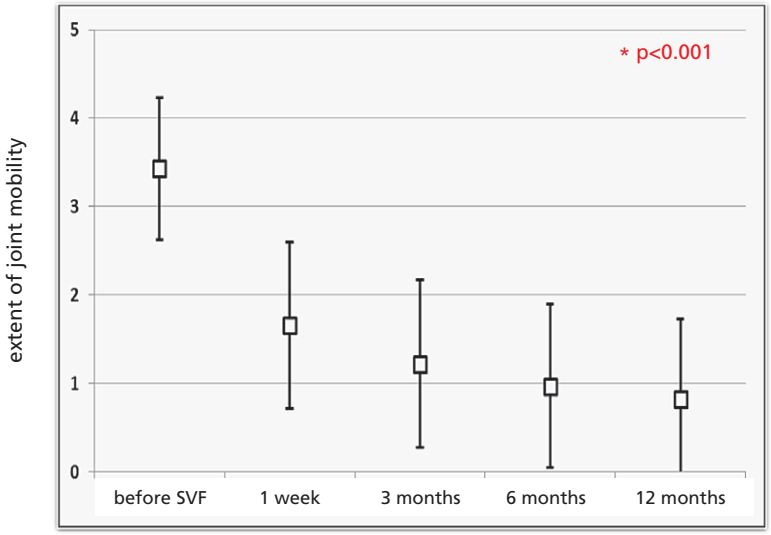
Limping



Grade of limping

0 no limping
1 less frequent minor limping
2 frequent minor limping
3 moderate limping
4 severe limping
5 impossible to walk

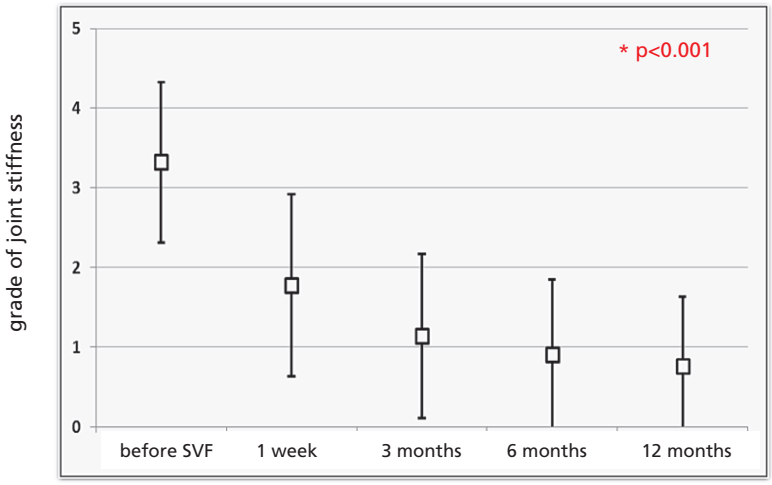
Extent of joint mobility



Extent of joint mobility

0 no limitation
1 up to 20 % limitation
2 at least 21 % and up to 40 % limitation
3 at least 41 % and up to 60 % limitation
4 at least 61 % and up to 80 % limitation
5 more than 80 % limitation

Joint stiffness



Grade of joint stiffness

0 no stiffness
1 minor stiffness
2 moderate stiffness
3 serious stiffness
4 severe stiffness
5 impossible to walk

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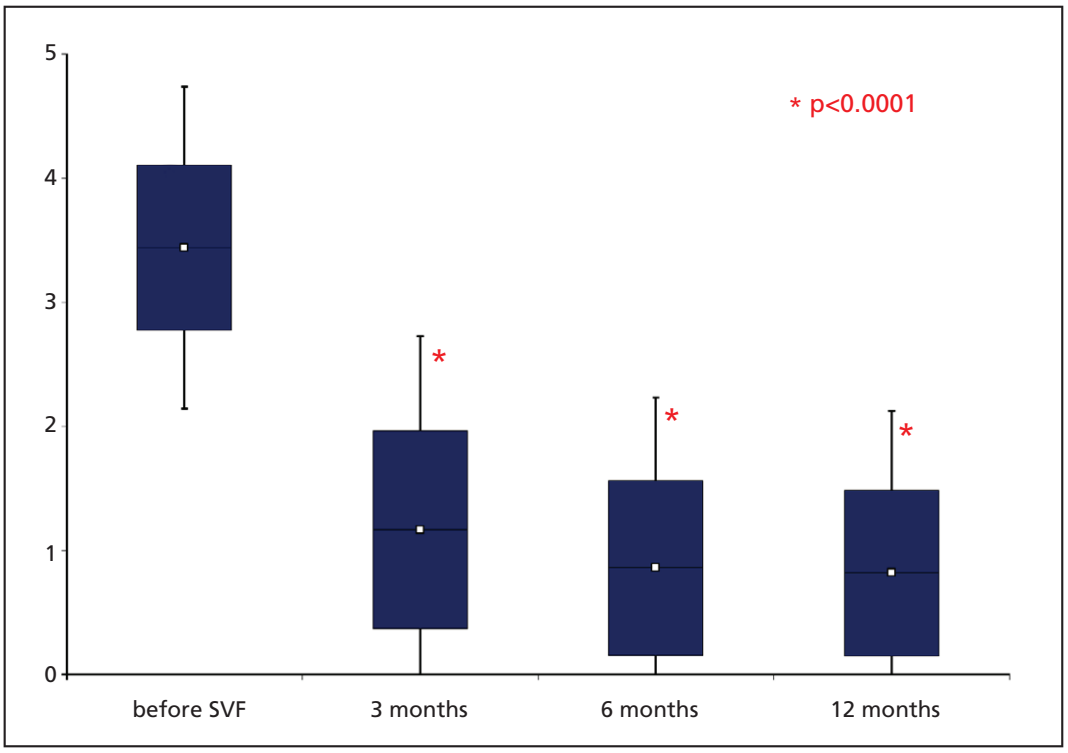
Modified KOOS/HOOS Score

Modified KOOS/HOOS clinical score was used to evaluate clinical effect.

A calculation of the score is based on 5 parameters:

- **Pain**
- **Number of painkillers per week**
- **Limping at walk**
- **Extent of joint movement**
- **Stiffness**



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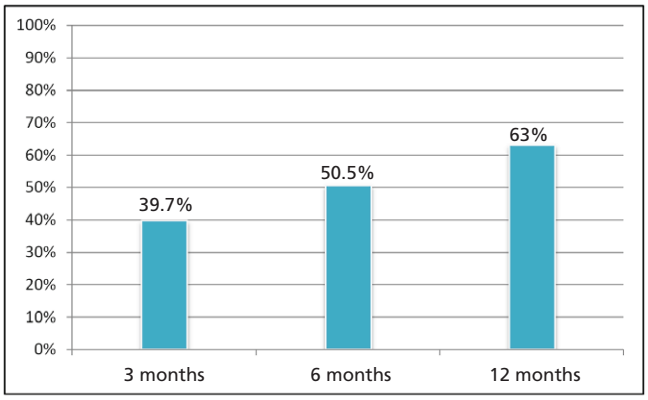
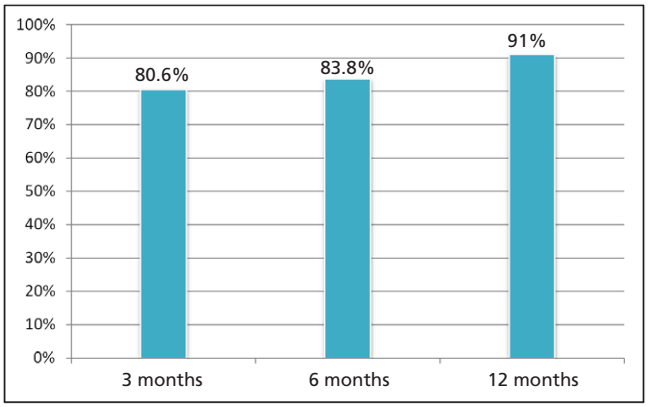
Modified KOOS/HOOS Score

Clinical evaluation shows 75% and 50% score improvement, or worsening of the score. Score is evaluated 3, 6 and 12 months after SVF cell therapy.

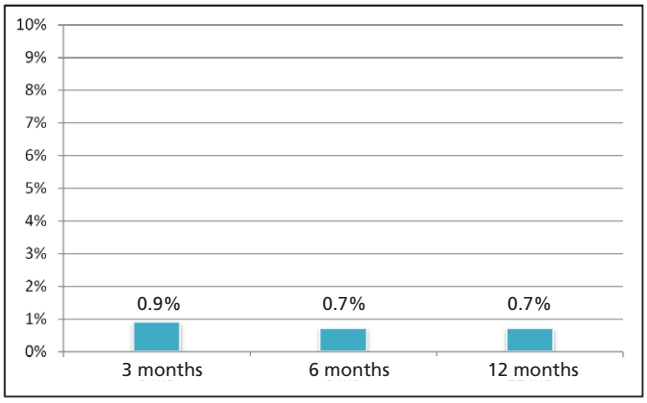
75% score improvement



50% score improvement



Score worsened

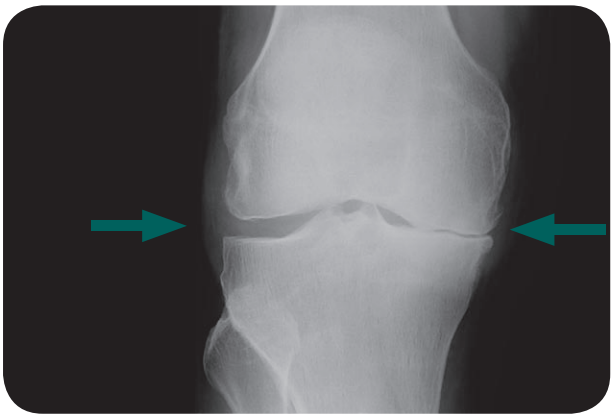


Case History I: Right Knee Osteoarthritis

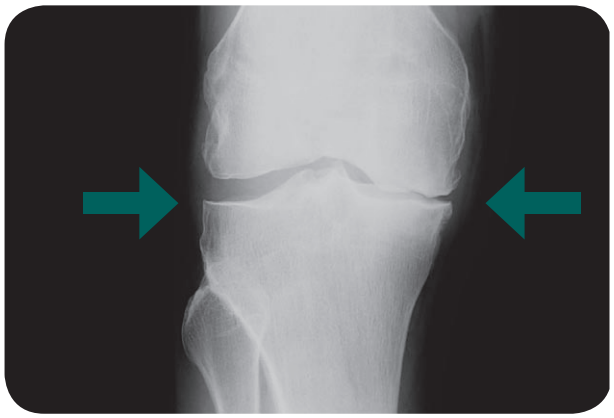
- 56 years old male with grade III gonarthritis (according to the Kellgren-Lawrence classification)
- weight 88 kg, height 176 cm
- kissing bone phenomena in medial compartment
- X-ray results 12 months after SVF cell therapy show greater cartilage amount in medial compartment

X-ray results:

before SVF cell therapy



12 months after SVF cell therapy

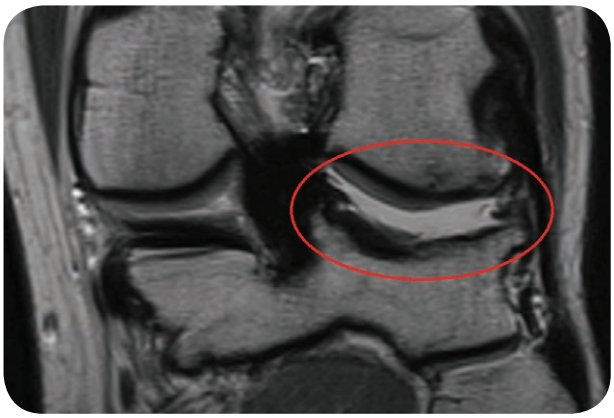


Case History II: Osteoarthritis and Lateral Femoral Condyle Osteochondronecrosis

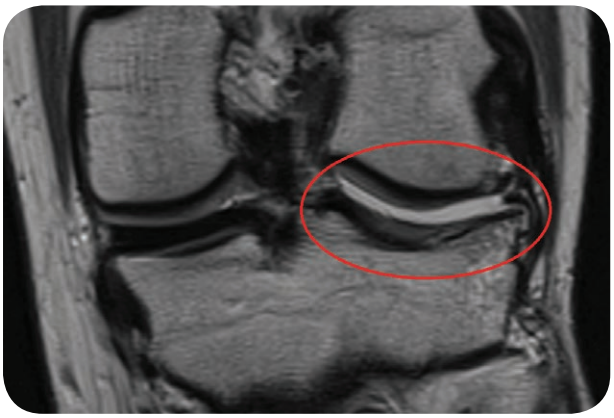
- 45 years old male with grade II OA
- weight 82 kg, height 178 cm
- lateral femoral condyle osteochondronecrosis with a diameter 7 mm
- 6 months after SVF cell therapy defect size decreased to 3 mm in diameter; relief of pain and regression of clinical problems

NMR results:

before SVF cell therapy



6 months after SVF cell therapy



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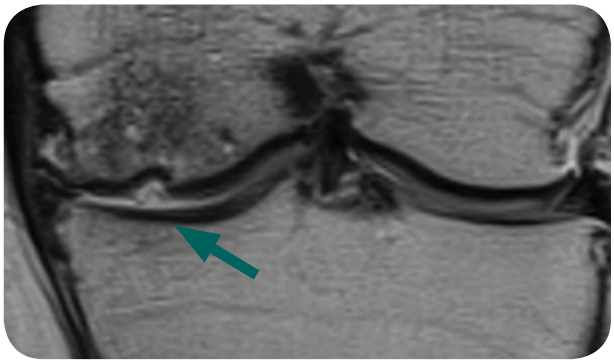
Case History III: Osteoarthritis and Subchondral Cortical Defect

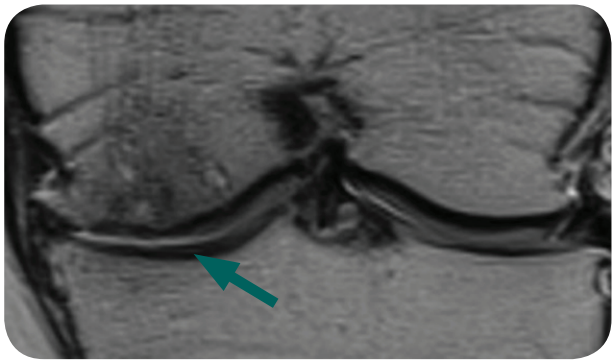
- 49 years old male with grade II – III gonarthritis
- subchondral cortical defect
- 14 months after SVF cell therapy were observed cartilage surface smoothening and healing of subchondral defect
- dramatic clinical improvement is accompanied by cartilage regeneration

NMR results:

before SVF cell therapy



14 months after SVF cell therapy

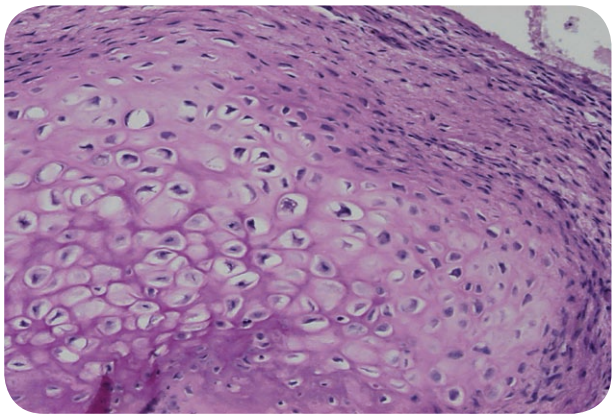


Case History IV: Cartilage Regeneration Documented in a Patient with Grade III Hip Osteoarthritis

- 52 years old female with grade III coxarthritis
- significant clinical improvement
- cartilage regeneration is histologically verified

Result of histological analysis (HE staining):

12 months after SVF therapy



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Side Effects of Cell Therapy

No serious side effects including heart attack, stroke, embolism, infection or tumor formation were observed in 1114 patients treated with SVF cell therapy. Only minor side effects were reported.

Serious side effects	No.
Myocardial infarction	0
Stroke	0
Thromboembolism	0
Systemic infection	0
Cancer	0
Death	0
Other serious side effect	0

Other side effects	No. (%)
Local pain < 24 hours	47 (4.22)
Local pain > 24 hours *	38 (3.41)
Local swelling < 72 hours	58 (5.21)
Local swelling > 72 hours	12 (1.08)
Fever > 38°C < 24 hours	9 (0.81)
Fever > 38°C > 24 hours **	4 (0.36)
Reactive synovitis	5 (0.45)
Headache	3 (0.27)
Deep venous thrombosis	2 (0.18)
Infectious synovitis ***	1 (0.09)

* pain persisting for more than 24 hours
** fever above 38 °C lasting for more than 24 hours
*** one patient experienced infectious synovitis that was unlikely related to SVF therapy, but it is impossible to completely exclude it

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Comparison of Standard Therapy with Cell Therapy

	Artificial joint replacement	SVF therapy
Availability	limited by age, medical condition	unlimited
Anesthesia	general	local
Serious complications	death, infection, thromboembolism, stroke, heart attack	none
Number of joints treated during 1 procedure	1	1– 4
Rehabilitation	3 – 6 months	1 week
Long-term sequelae	wearing of the artificial joint	not known yet

Medical service – Processing Fat Tissue and Isolation of SVF Containing the Stem Cells

Use: isolation of SVF cells from the fat tissue by trained personnel of Cellthera Ltd. company.

Applications: autologous stem cell therapy.

Source of cells: fat tissue obtained by liposuction.

Medical service contains: laboratory processing of the fat tissue, isolation of SVF containing the stem cells and preparation of cell suspension ready for direct administration to the patient by trained personnel of Cellthera Ltd. company.

Equipment needed: laboratory established according to the rules of good manufacturing practice equipped with laminar box, centrifuge and shaker/incubator device.

Scheme of the Procedure

Tumescent liposuction

Laboratory processing of lipoaspirate and isolation of SVF containing the stem cells

Lipoaspirate

Lipoaspirate washing

Homogenization

Isolation of SVF cells

Direct application of the SVF cell suspension containing the stem cells to the patient

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Contact us

At Cellthera, Ltd. we are pleased to share our experience from the area of cell therapies with your team. Our experts are ready to train your clinical specialists either in the Czech Republic or on site. Please, contact us for pricing information.

Technical and customer support is available 24 hours a day, 7 days a week via e-mail support@cellthera.org or by phone.

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