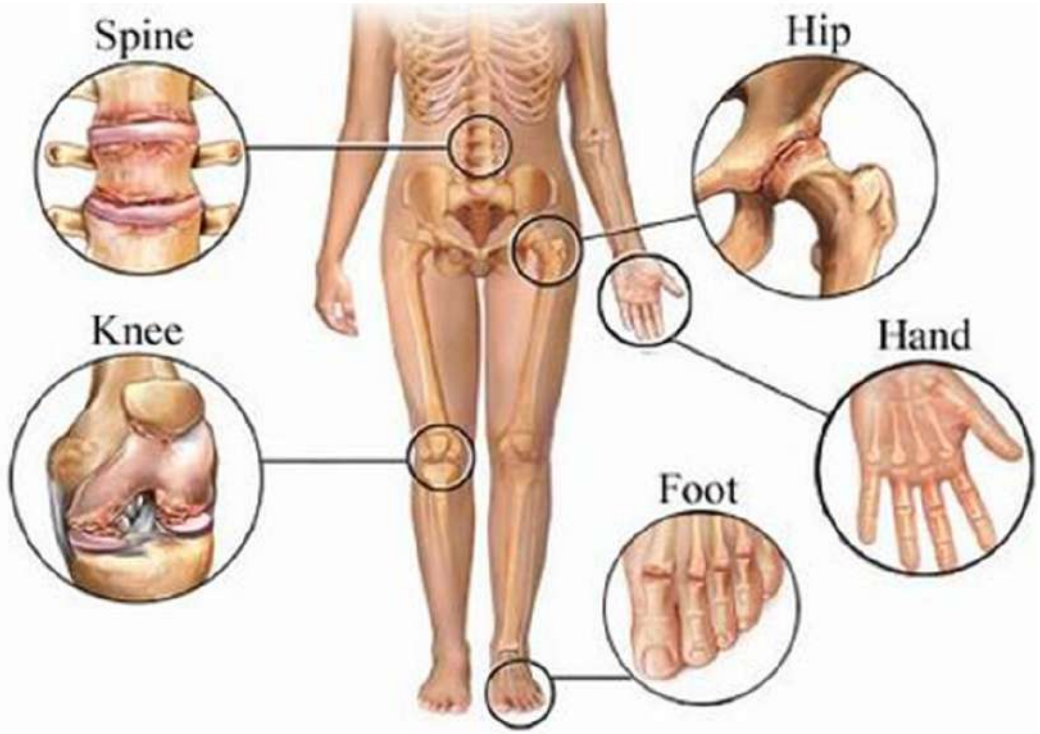
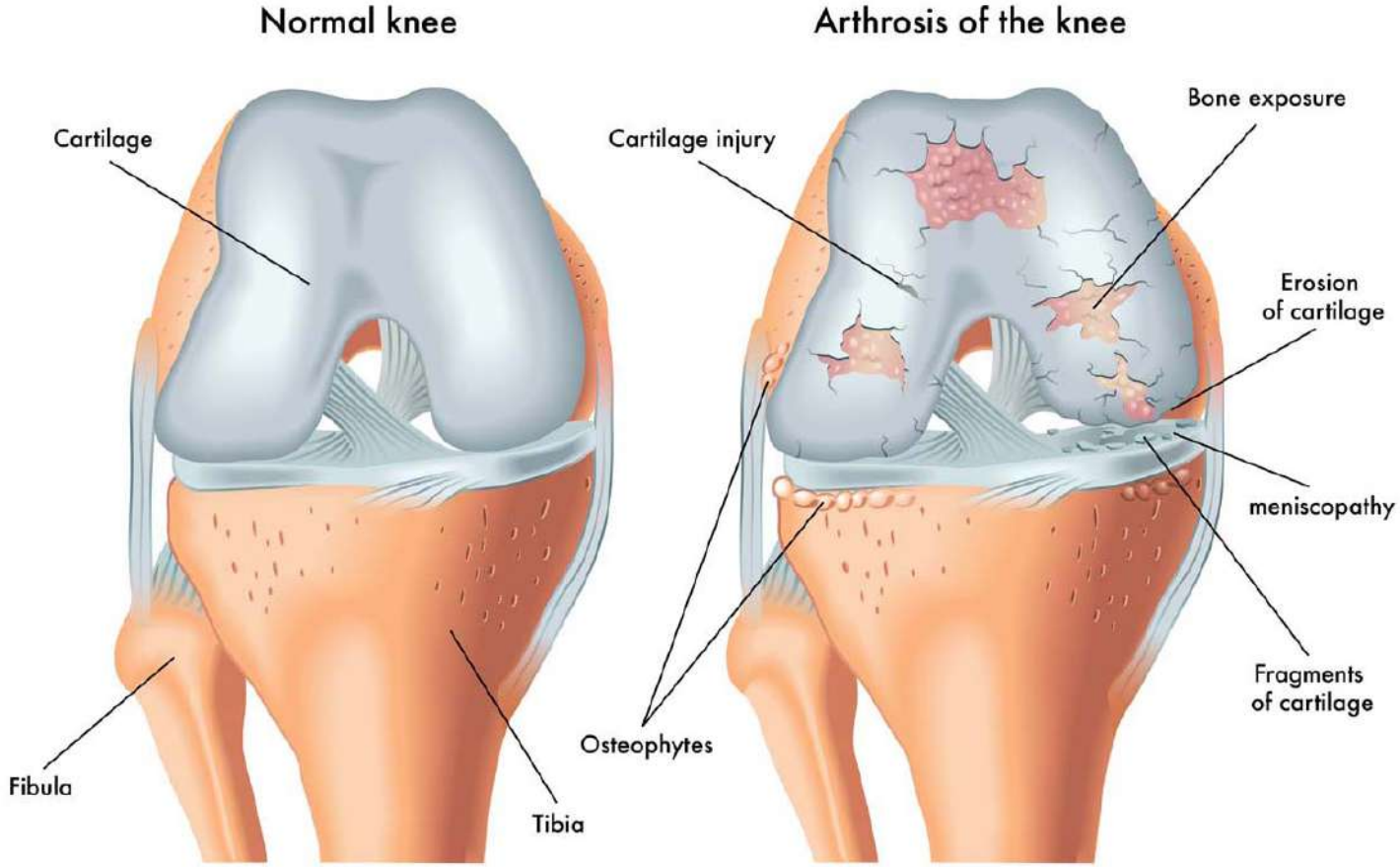
Efficacy of Stem Cell-Rich SVF - Stromal Vascular Fraction Fluid In Treating Osteoarthritis

Dr.Aşkın Nasırcılar, MD

OSTEOARTHRITIS (OA)

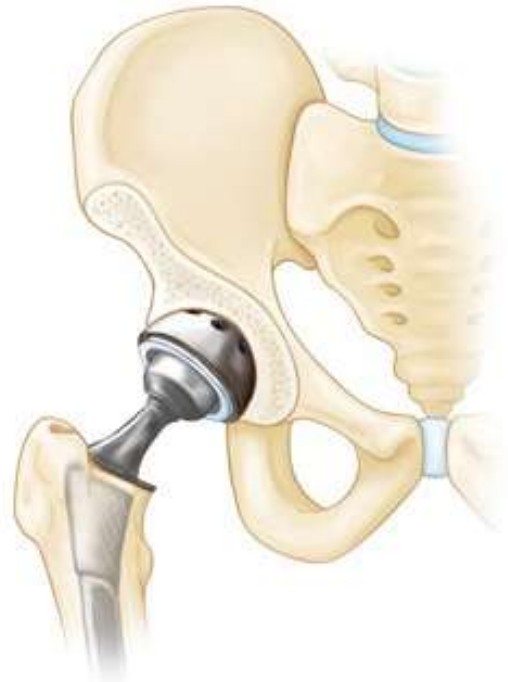
- Degenerative process of joint's cartilage.
- Most common joint disease worldwide.





OSTEOARTHRITIS (OA)

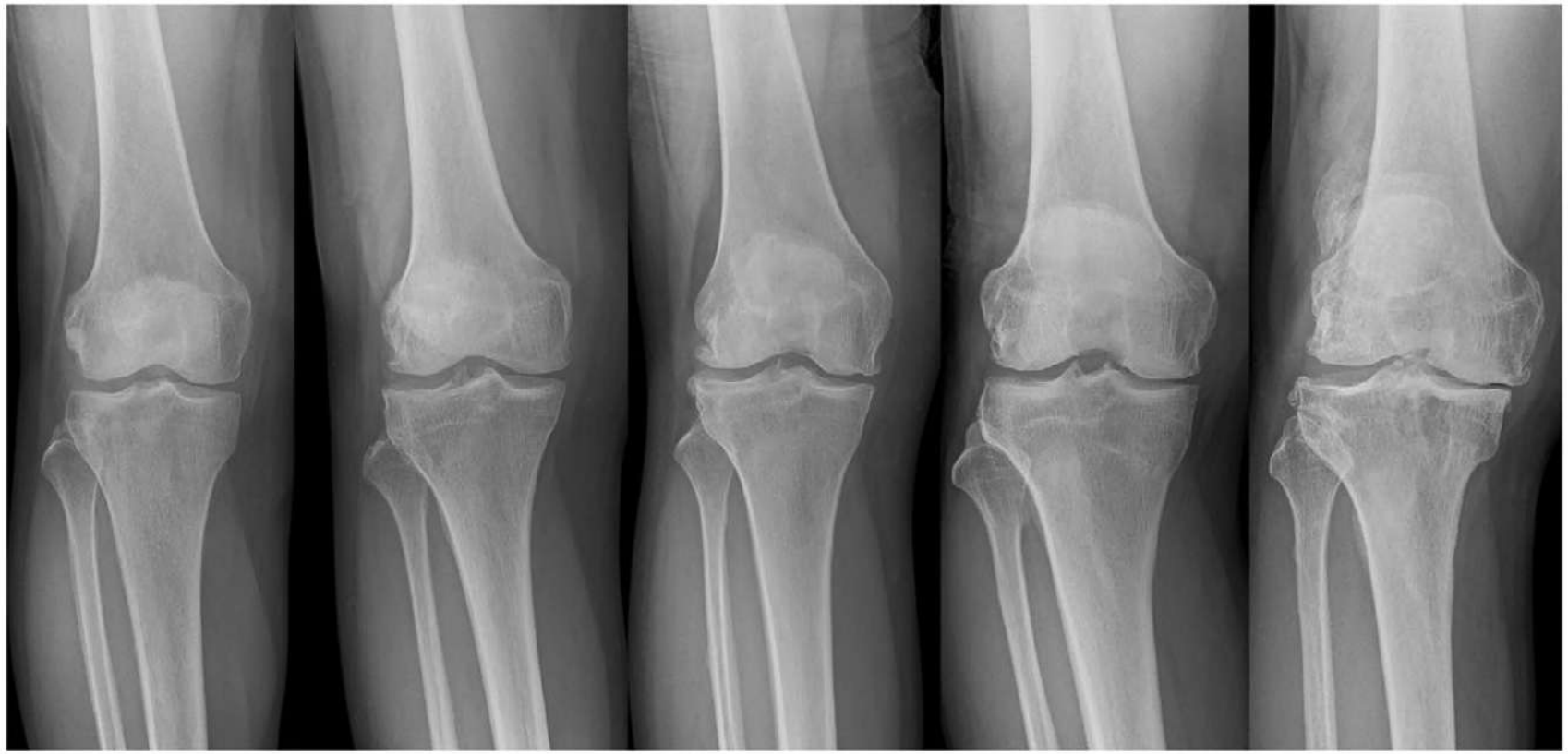
- No effective or curative treatment of disease progression.
- Severe cases mostly require surgery at the end.



Kellgren and Lawrence System for Classification of Osteoarthritis

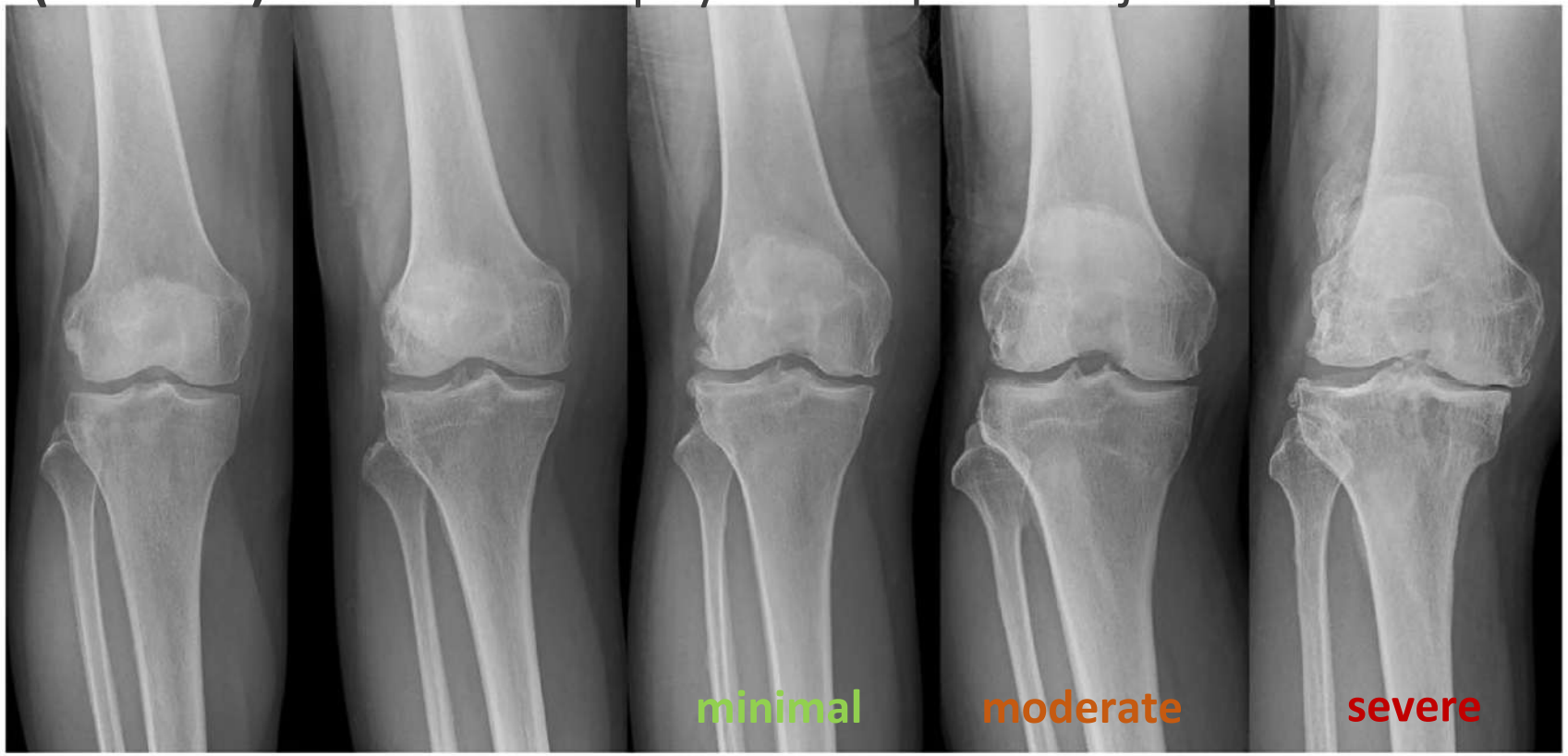
- A common method of classifying the severity of osteoarthritis (OA) using **five grades.**

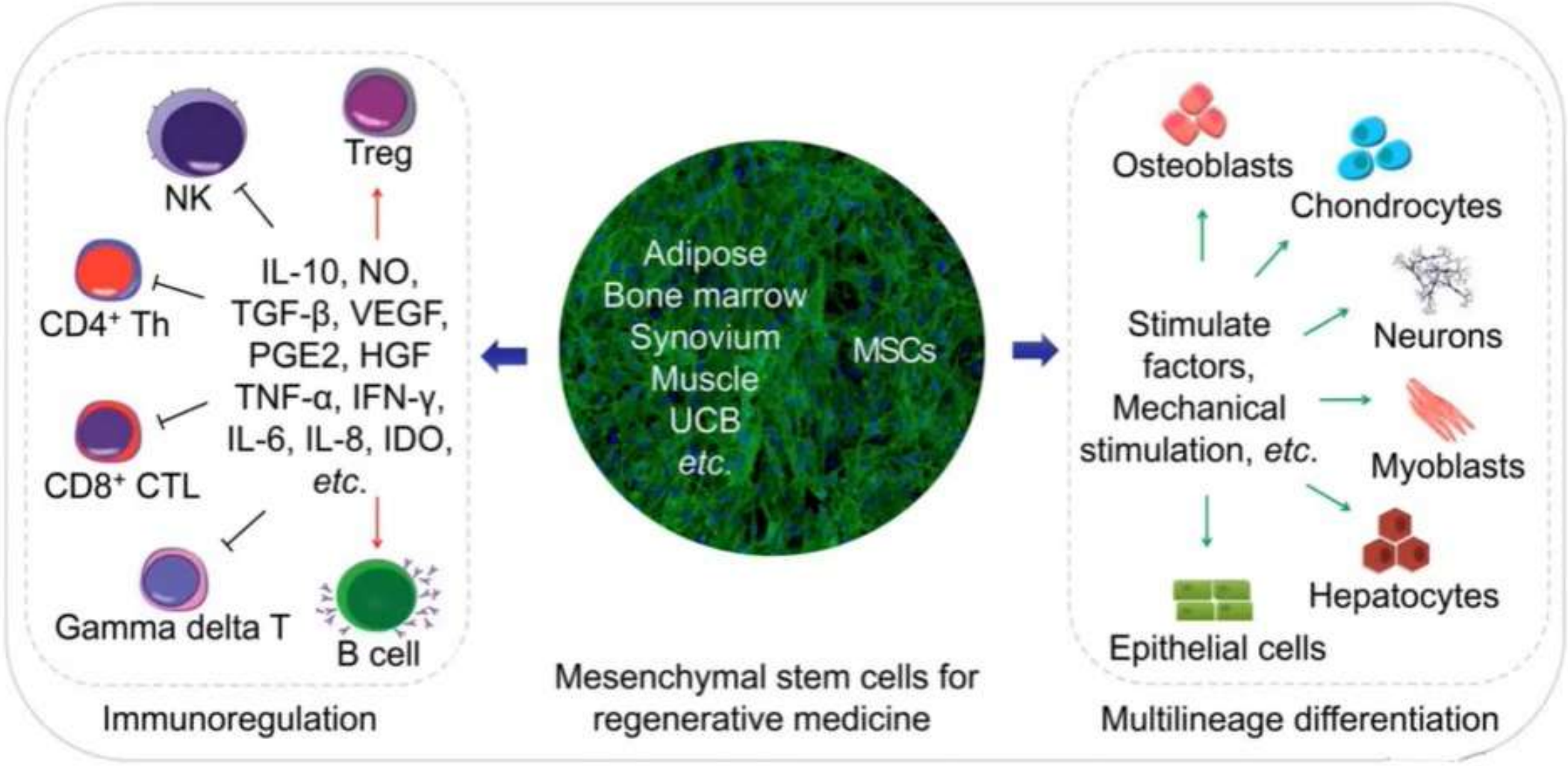
Kellgren J & Lawrence J. Radiological Assessment of Osteo-Arthrosis. Ann Rheum Dis. 1957;16(4):494-502.



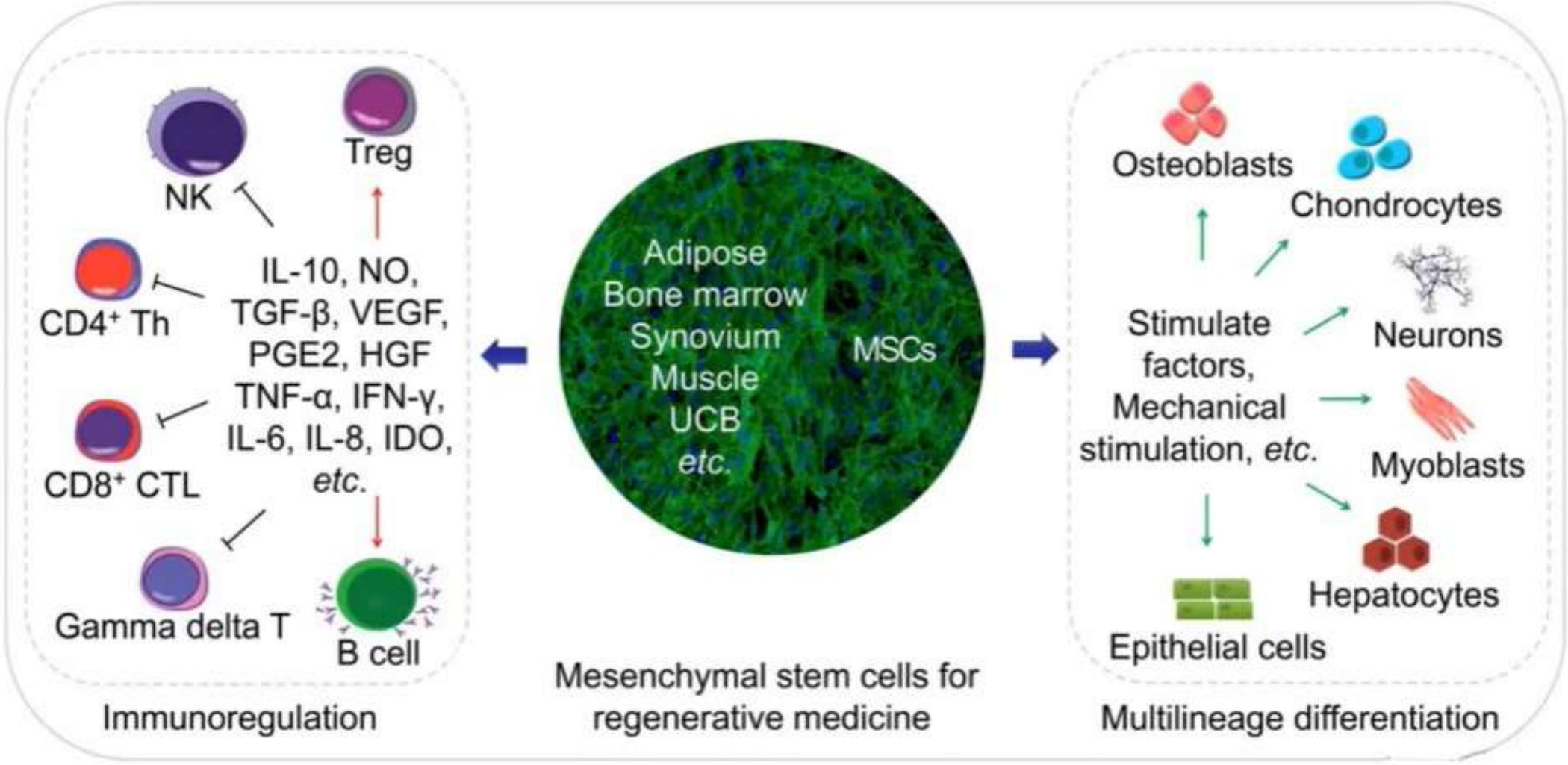
Kellgren and Lawrence System for Classification of Osteoarthritis

- Osteoarthritis is deemed present at grade 2 although of minimal severity.
- **Grade 2 (minimal)**: definite osteophytes and possible joint space narrowing

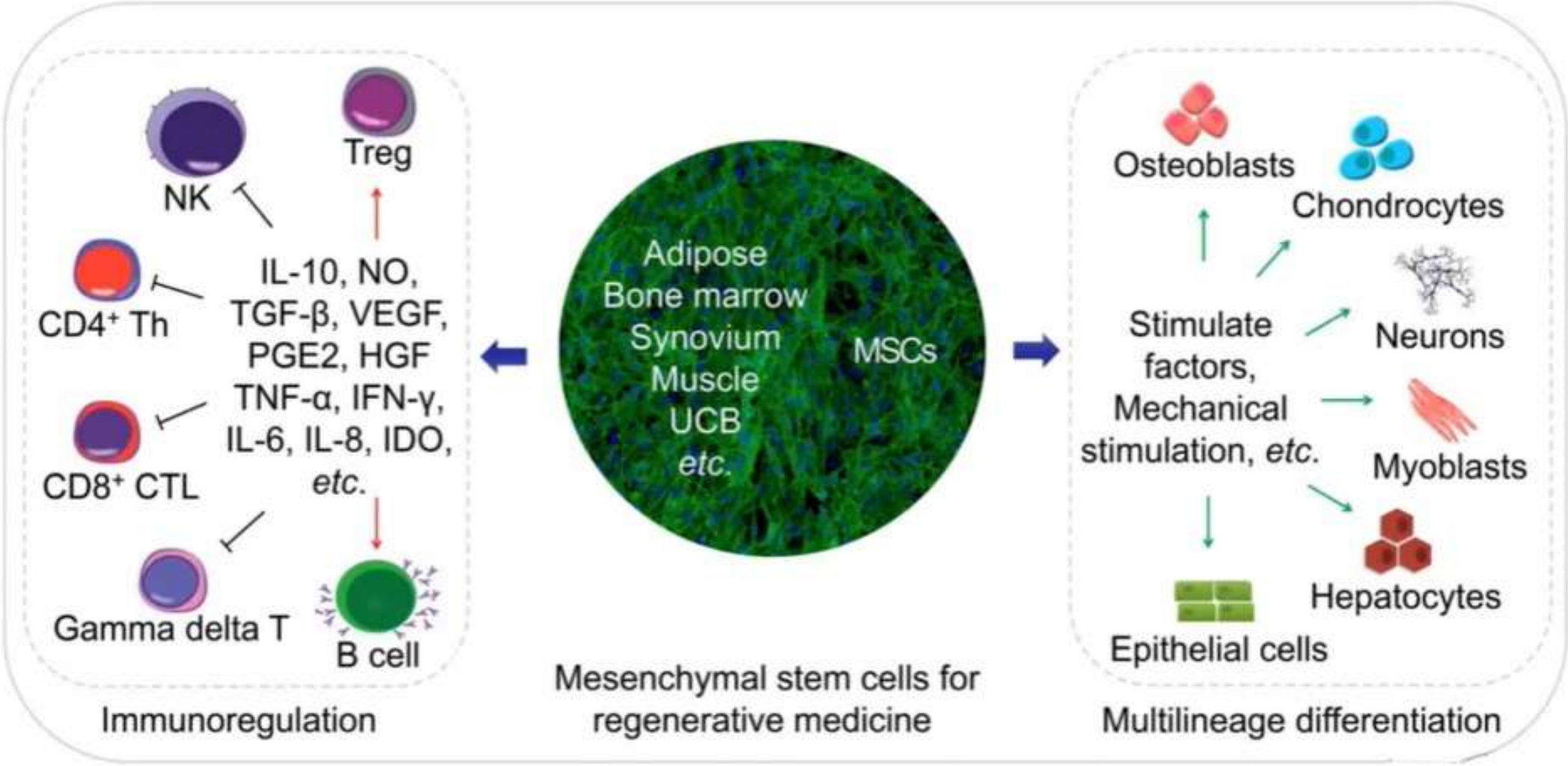




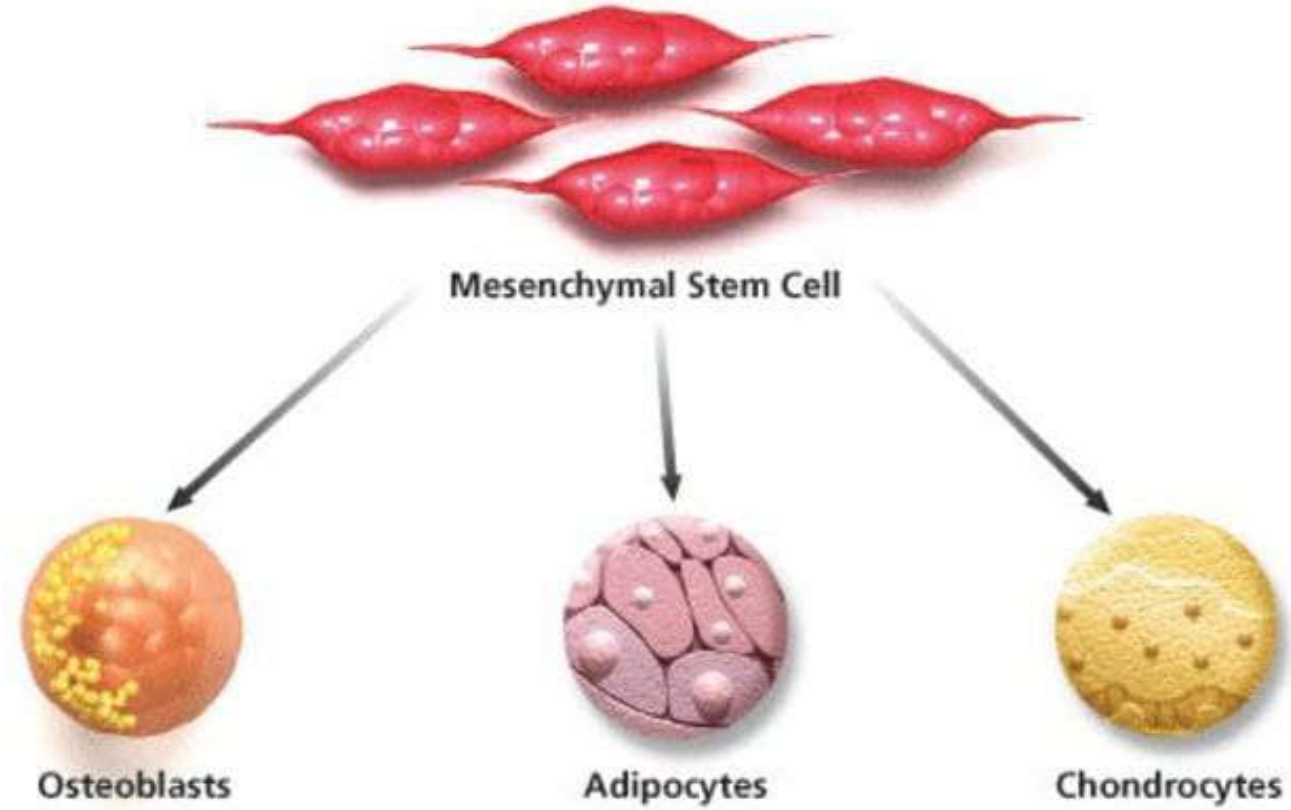
- Recently, cell-based therapies have emerged as possible disease-modifying treatments.



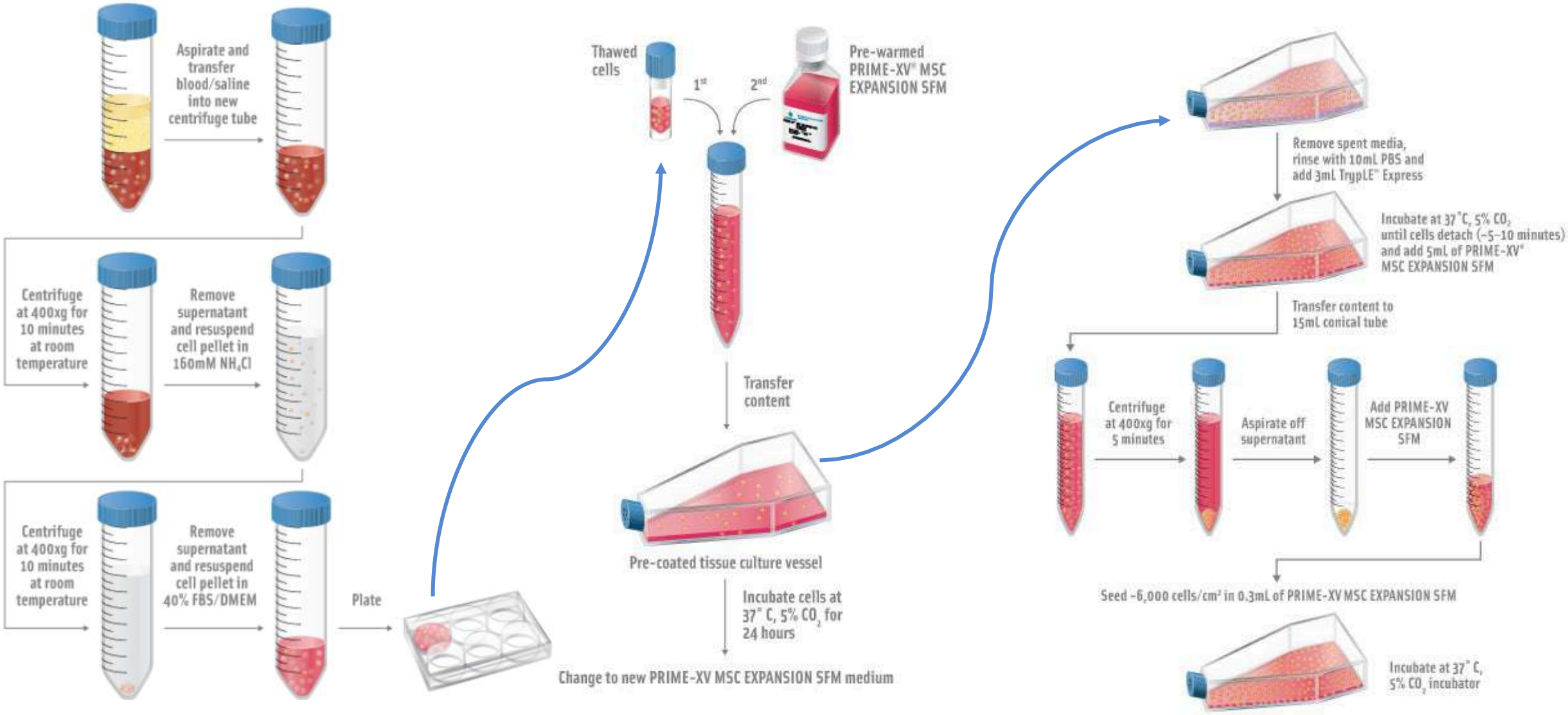
- Recently, cell-based therapies have emerged as possible disease-modifying treatments.
- Mesenchymal stem cells (MSCs) have gained popularity due to their regenerative, anti-inflammatory, anti-apoptotic and anti-fibrotic properties.



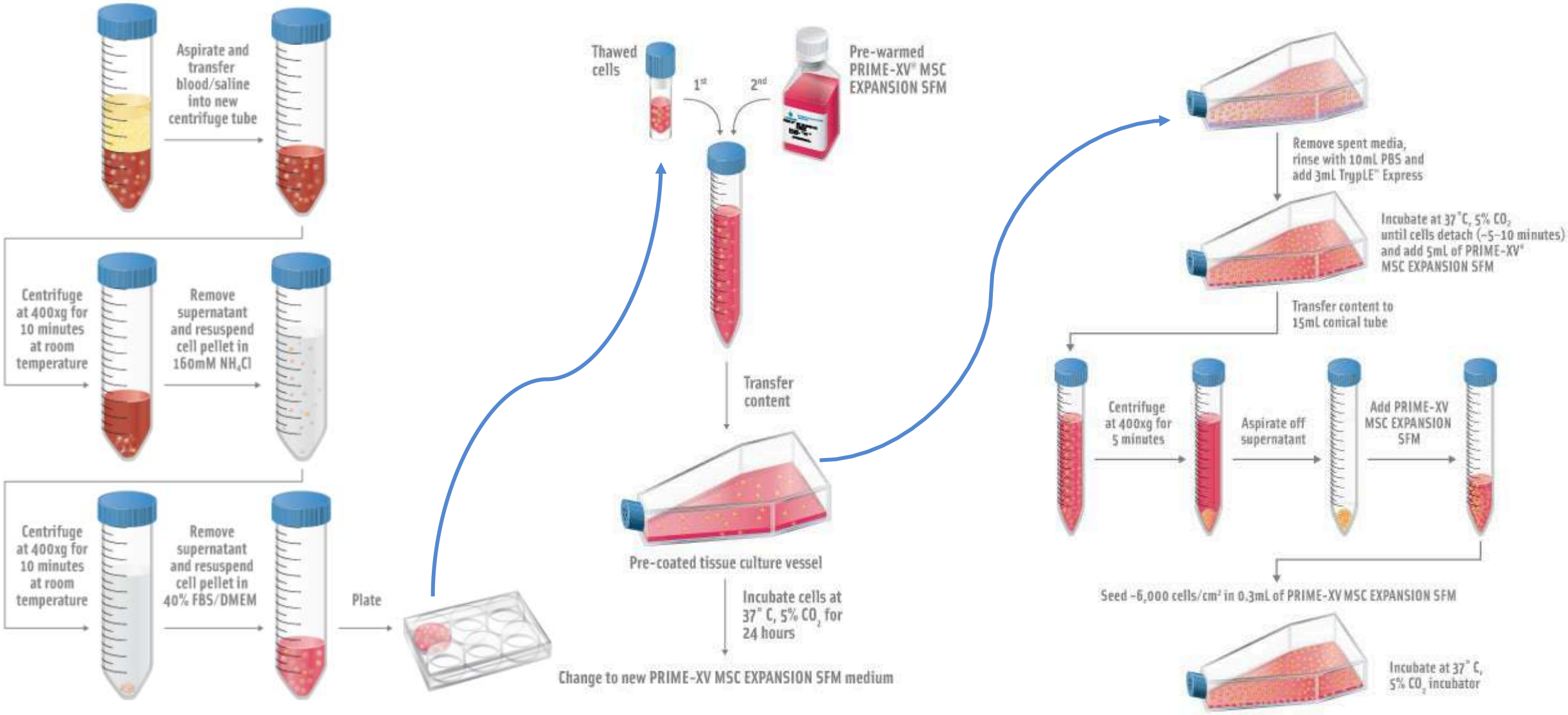
- Adipose-derived stem cells (ASCs) is an alternative to bone marrow-derived mesenchymal stem cells (BMMSCs), ASCs can be isolated from subcutaneous fat tissue more easily and in large quantities up to 1000 times the yield of bone marrow isolation.



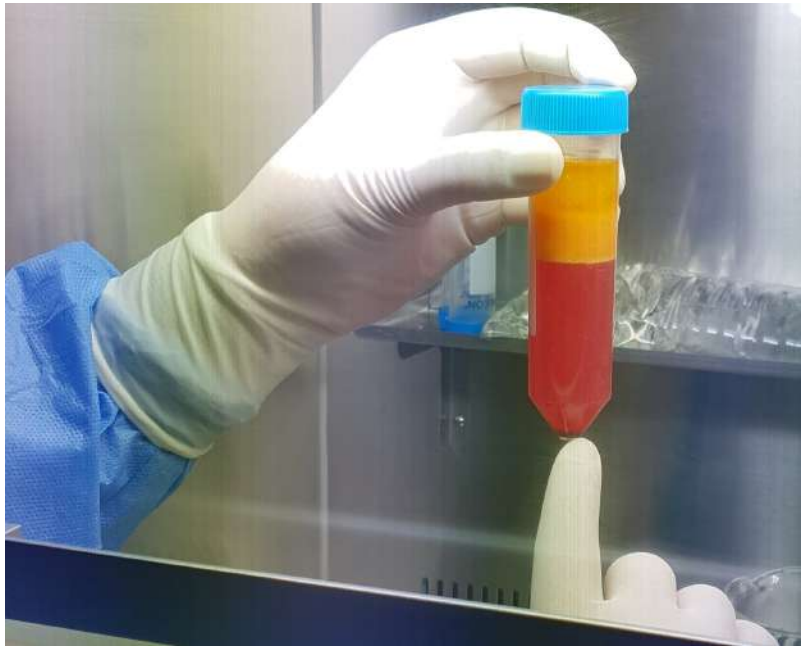
- These ASCs are multipotent stromal cells and must have the ability to differentiate into;.
  - osteoblasts,
  - chondrocytes,
  - adipocytes.



- However, the isolation of MSCs and ASCs may require multiple weeks and special laboratories for cell expansion.



- However, the isolation of MSCs and ASCs may require multiple weeks and special laboratories for cell expansion.
- A more efficient method for collection and administration of ASCs is the use of autologous stromal vascular fraction (SVF) cells.



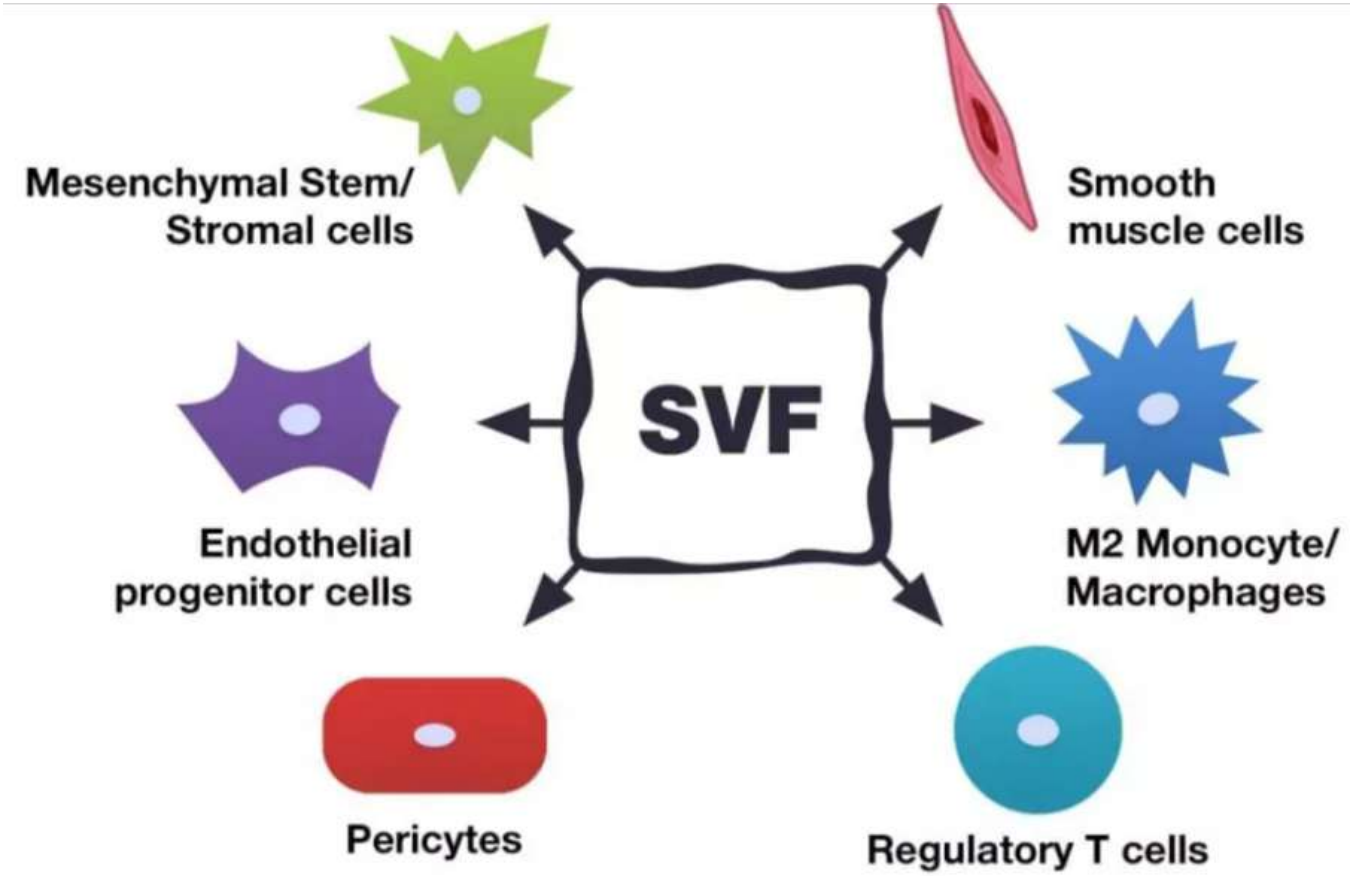
- SVF processing does not require cell expansion or cultivation.

- SVF can be processed at the bedside within a few hours.

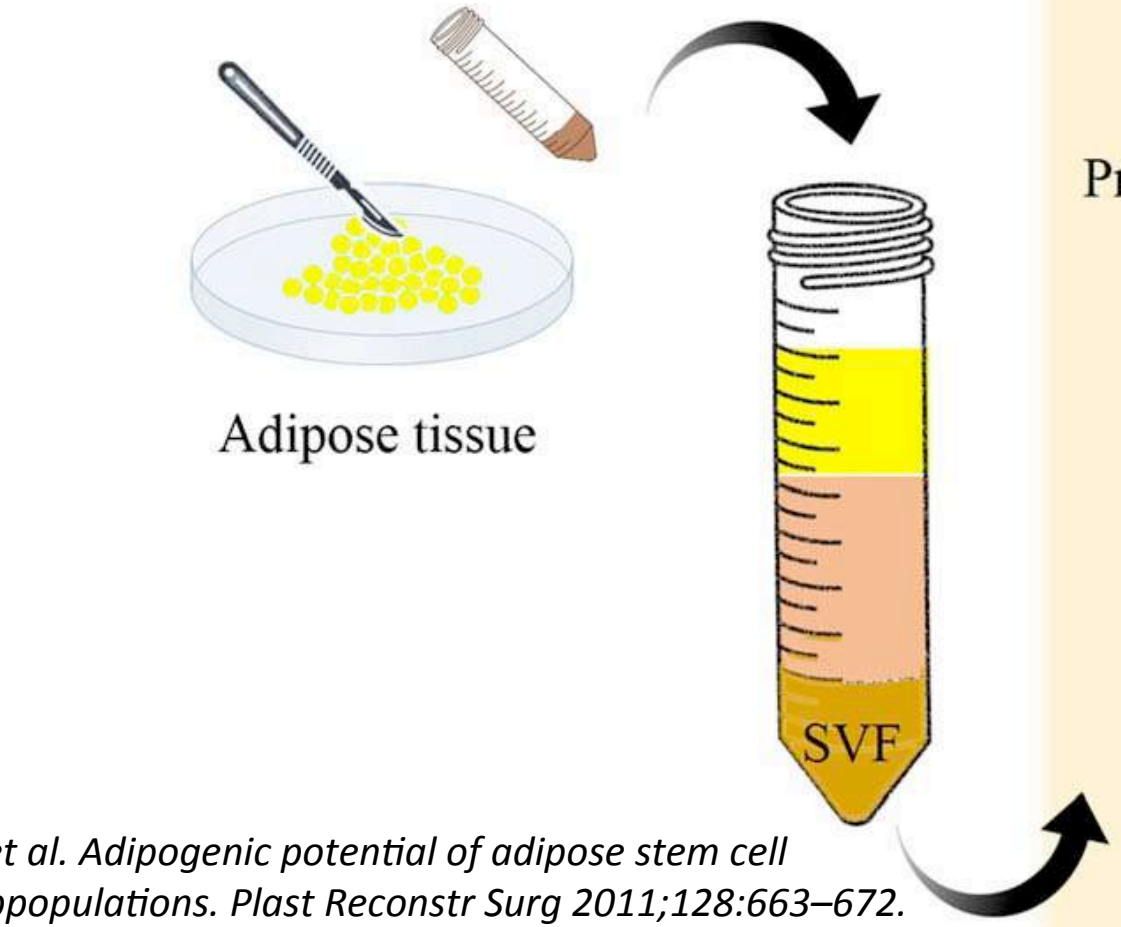
Jeyaraman M, Muthu S, Ganie PA. Does the Source of Mesenchymal Stem Cell Have an Effect in the Management of Osteoarthritis of the Knee? Cartilage 2021; 13: AAAA1532-1547

What is SVF?

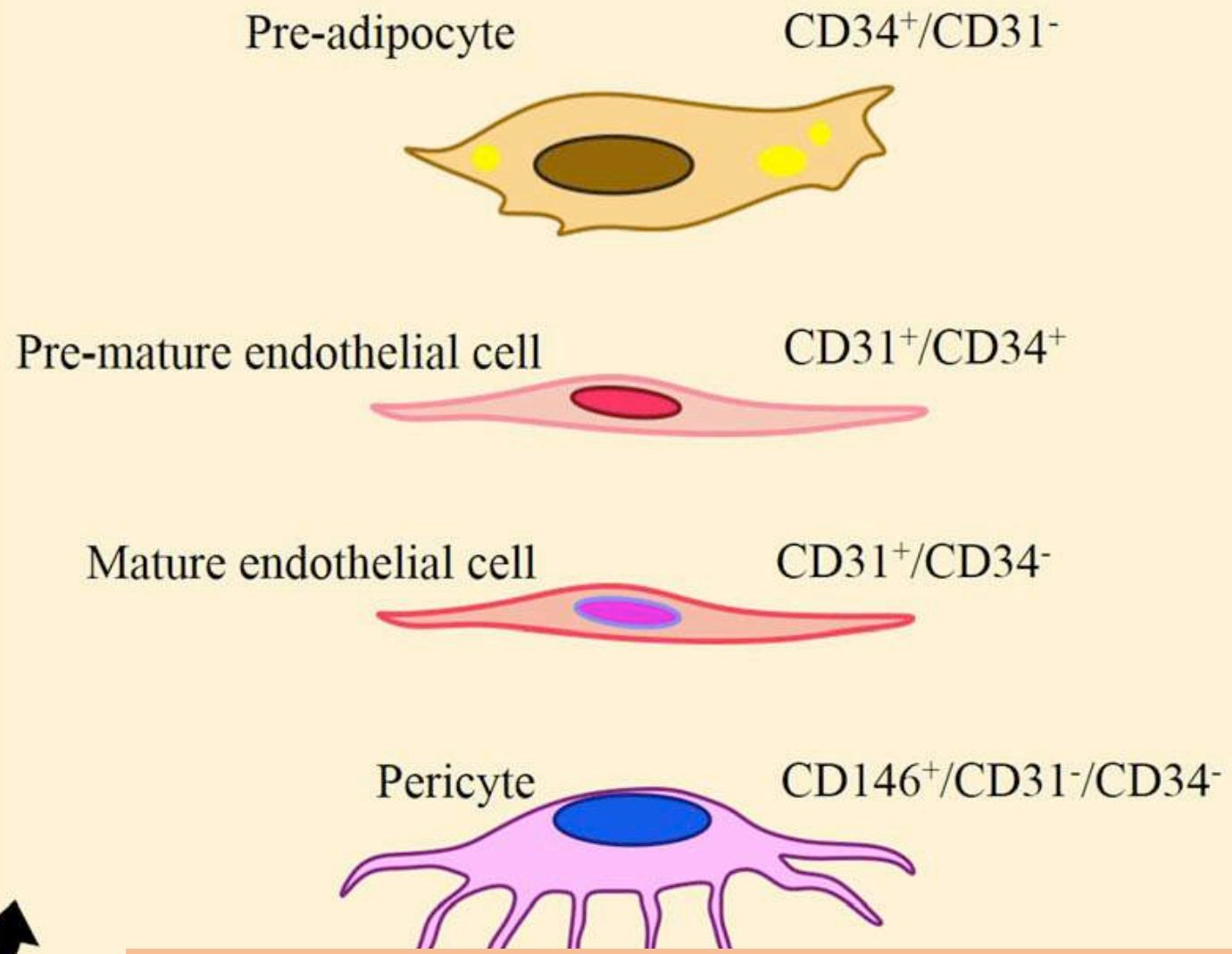
- SVF is a lipid-free mixture of cell lineages including;
  - circulating blood cells,
  - immune cells
  - fibroblasts,
  - pericytes,
  - endothelial progenitor cells,
  - perivascular smooth muscle cells
  - ASCs and growth factors



- Four non- hematopoeitic, abundant cell populations with the majority of **pre-adipocyte** population within SVF.
- Often referred to as Adipose tissue derived Stem Cells (ASCs).

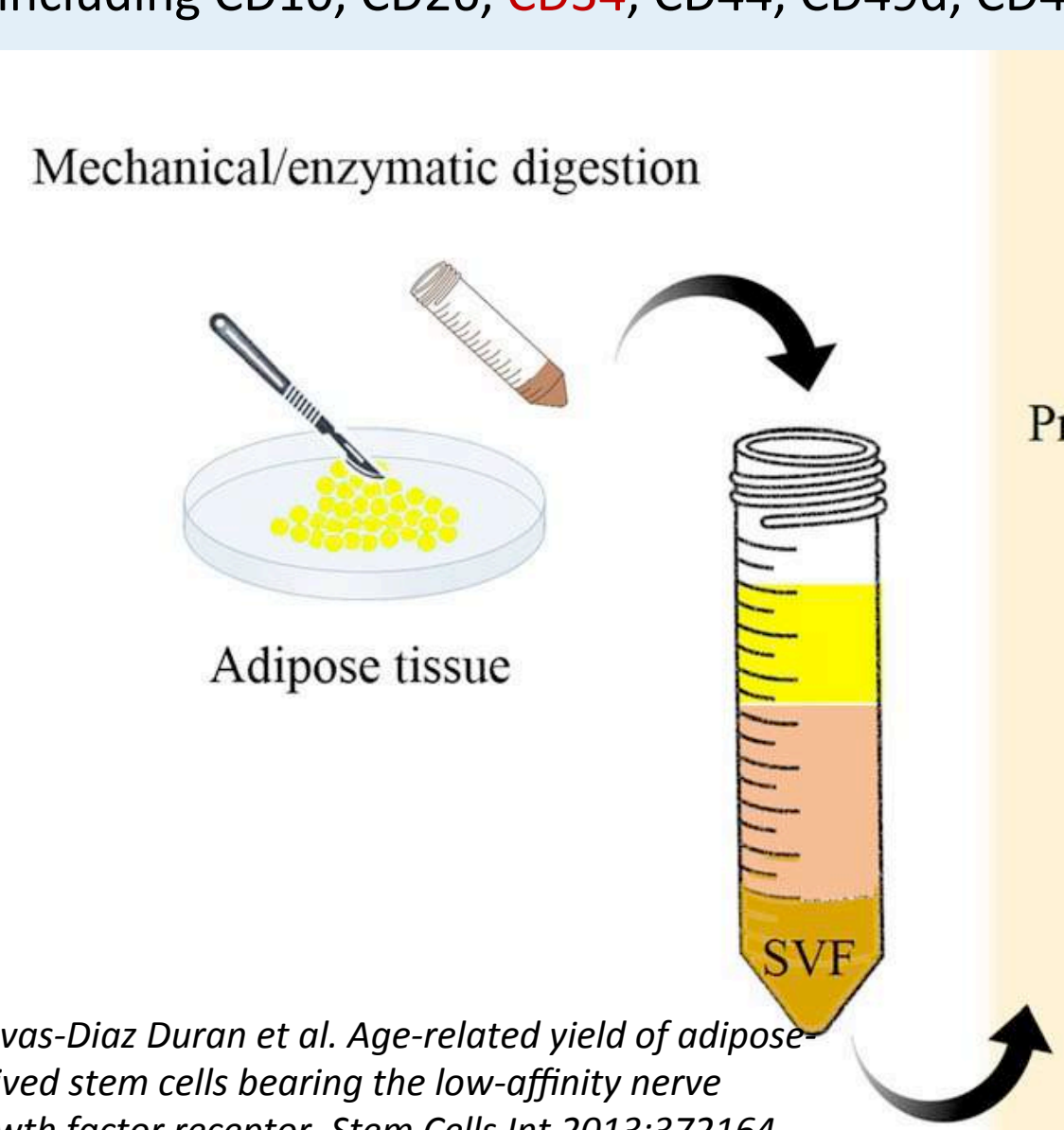


Li et al. Adipogenic potential of adipose stem cell subpopulations. Plast Reconstr Surg 2011;128:663–672.

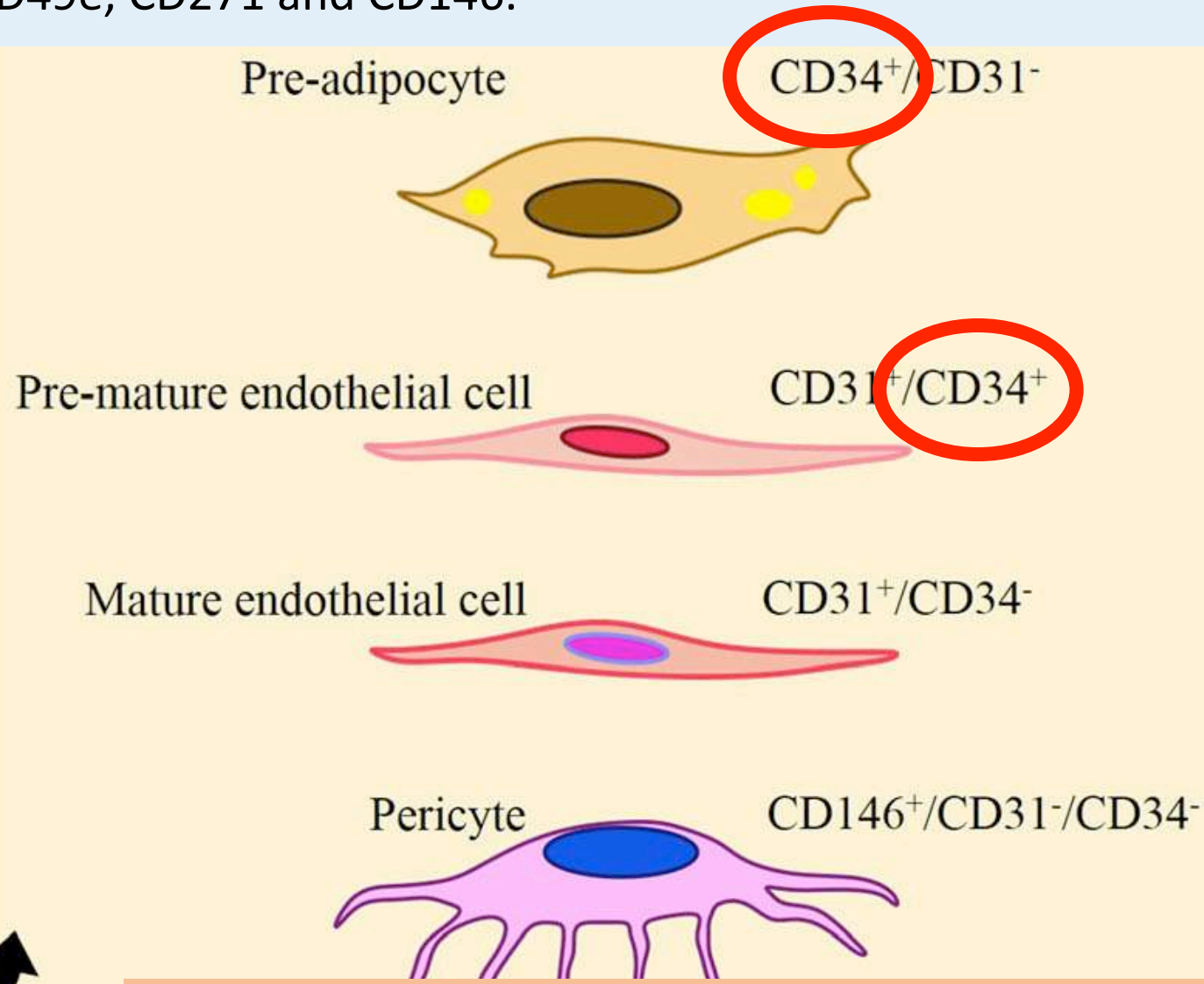


The cellular components of the SVF

- Do not follow the unique pattern of MSC surface markers (CD73, CD90, CD105 positive and CD11b, CD14, CD34, CD45 negative).
- Immunophenotype could be detected as CD13+, CD36+, and CD106- as well as variable markers including CD10, CD26, CD34, CD44, CD49d, CD49e, CD271 and CD146.



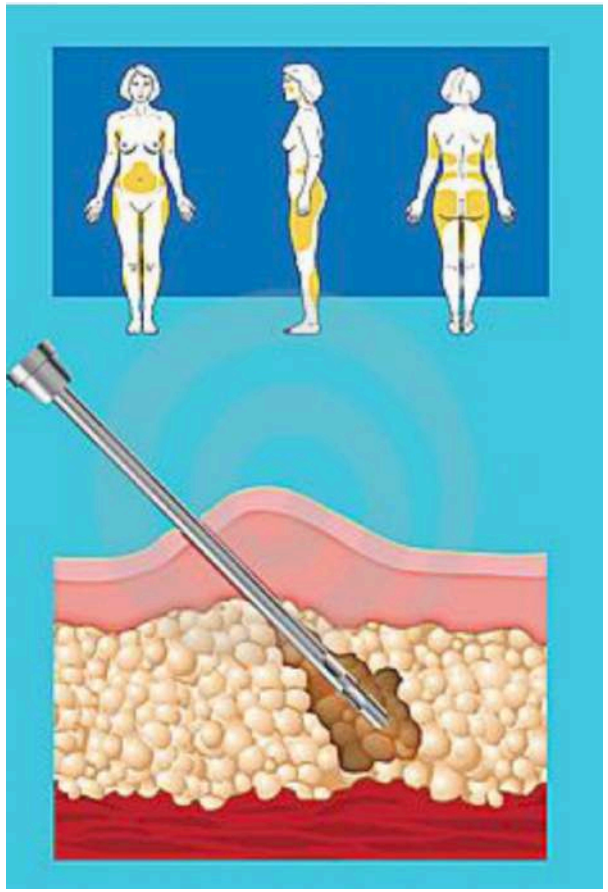
Cuevas-Diaz Duran et al. Age-related yield of adipose-derived stem cells bearing the low-affinity nerve growth factor receptor. Stem Cells Int 2013:372164.



The cellular components of the SVF

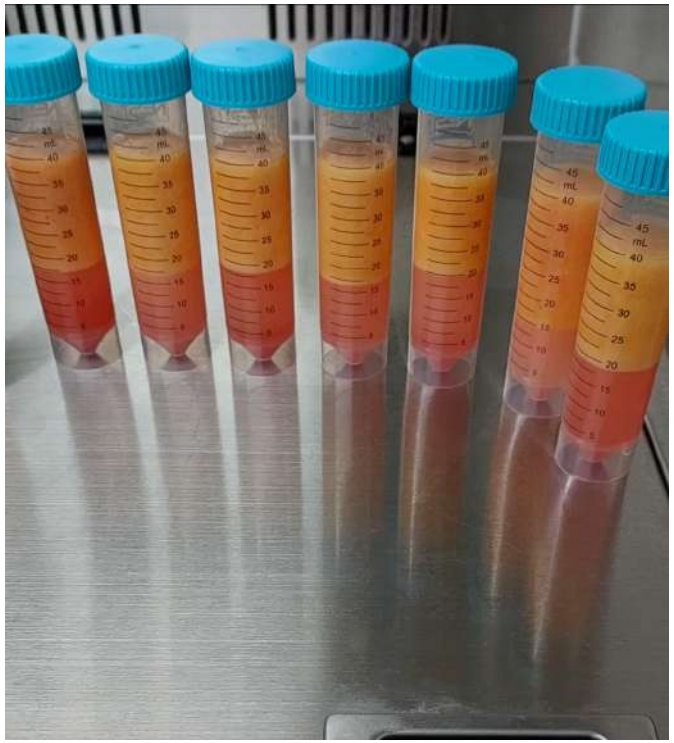
What is SVF?

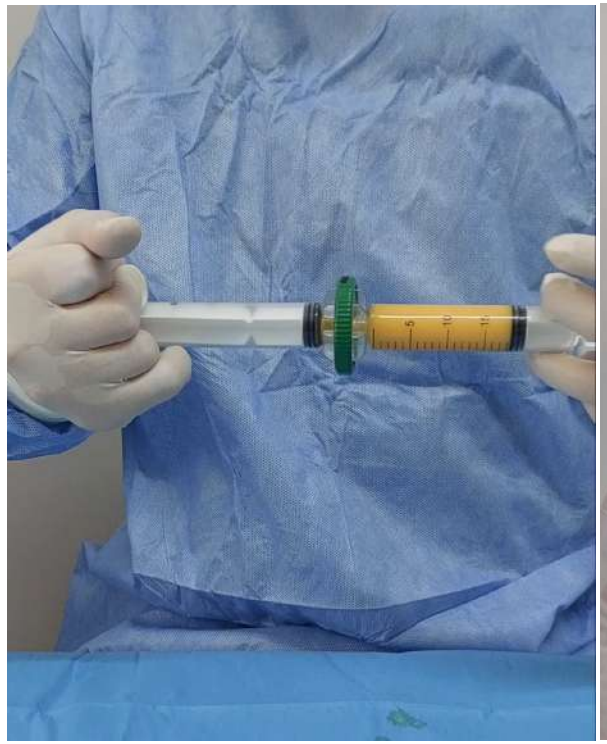
- The process begins with liposuction or lipoaspiration.



What is SVF?

- After collecting and washing the fat tissue, there are either mechanic or enzymatic ways to obtain Adipose-Derived Stromal Vascular Fraction (AD-SVFs).





What is SVF?

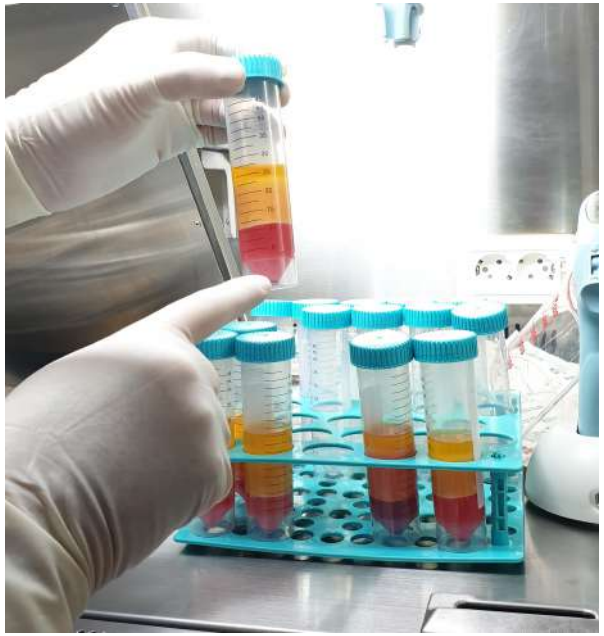
- SVF is typically obtained in one of **three ways**;

1- after centrifugation with enzymatic digestion (usually with collagenase),

What is SVF?

- SVF is typically obtained in one of **three ways**;

2- centrifugation and enzymatic digestion with the addition of mechanical separation (by a size-reduction filter),

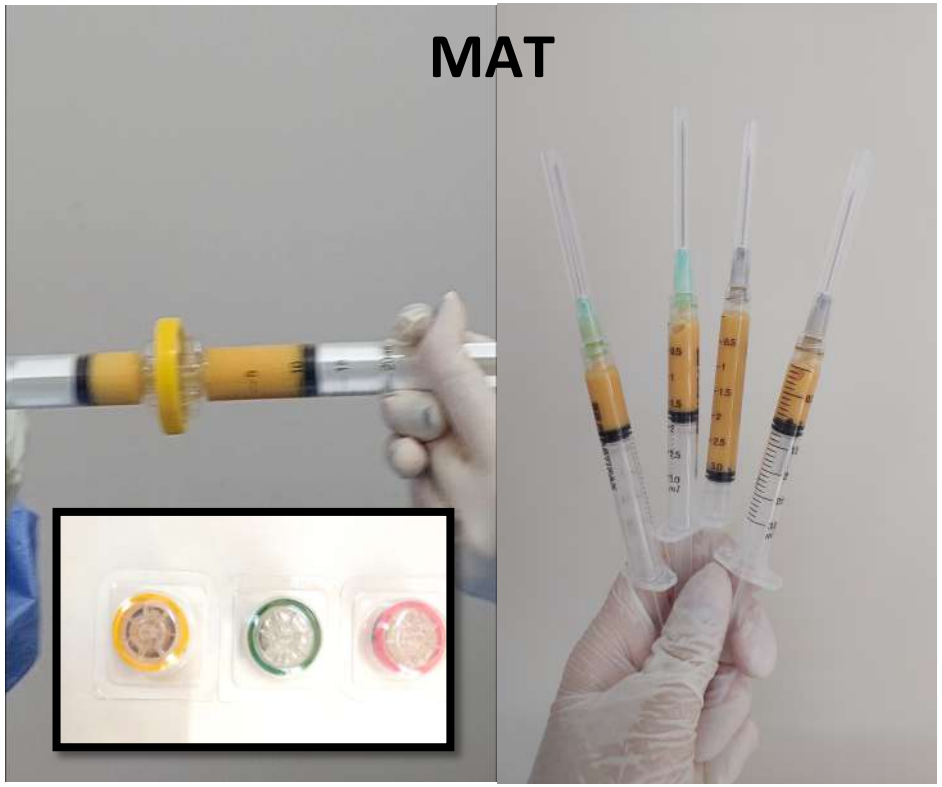


What is SVF?

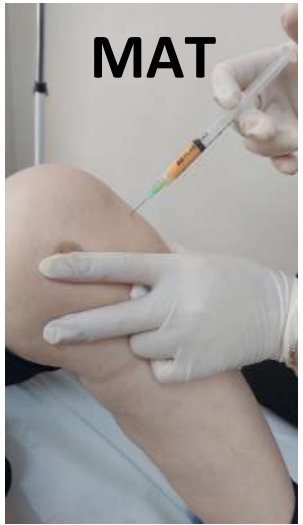
- SVF is typically obtained in one of **three ways**;

3- centrifugation and mechanical separation alone.

- This may called as **Micronized/Microfragmanted-SVF (MAT-SVF)**



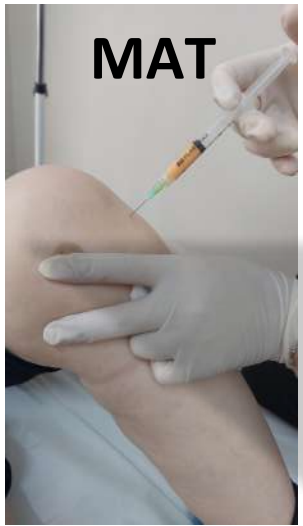

MAT


MAT


MAT-SVF


MAT-SVF


MAT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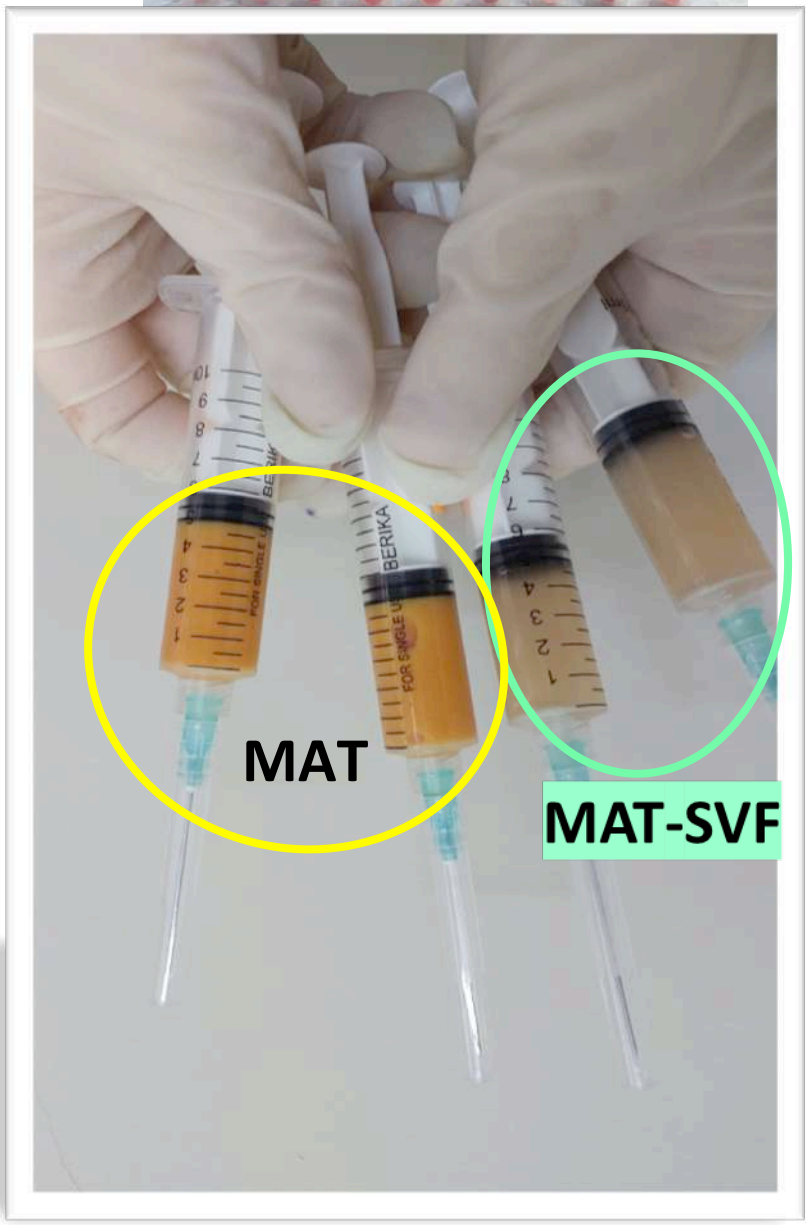
MAT
MAT-SVF


MAT-SVF


MAT-SVF

What is SVF?

Every method or system, clearly holds specific advantages and disadvantages

- **Mechanical techniques**
- low differentiative capability,
- high immunomodulatory effect through cytokines and growth factors release,
- simple, quick,
- generally not expensive.

- **Enzymatic methods;**
- high ability of differentiation,
- higher number of progenitor cells,
- more nucleated cells,
- more expensive.

CLINIC TRIALS

- Multiple studies have supported the use of intraarticular SVF injections.

- Improvement in knee OA symptoms ranging from 1 month to 2 years after SVF injection, without an increased risk of adverse effects.

The American Journal of Sports Medicine

Comparative Clinical Outcomes After Intra-articular Injection With Adipose-Derived Cultured Stem Cells or Noncultured Stromal Vascular Fraction for the Treatment of Knee Osteoarthritis

Naomasa Yokota,*† MD, Mari Hattori,* MD, Tadahiko Ohtsu
Masaki Otsuji,* MD, Stephen Lyman,‡ PhD, Kazunori Shimo
and Norimasa Nakamura,‖¶# MD, PhD, FRCS
Investigation performed at Tokyo Osteoarthritis Clinic Ginza

Background: Intra-articular injection of adipose-derived stem cells (ASCs) has s
tilage quality in the treatment of osteoarthritis (OA). However, while most precli
adherent ASCs, most clinical trials are being conducted with the stromal vascu
without prior culture.

Purpose: To directly compare clinical outcomes of intra-articular injection with

Study Design: Cohort study; Level of evidence, 3.

Methods: The authors retrospectively compared 6-month outcomes in 42 pati
with 12.75 million ASCs and 38 patients (69 knees) receiving a 5-mL preparation
2, 3, or 4 knee OA and had failed standard medical therapy. The visual analog sc
arthritis Outcome Score (KOOS) at baseline and 1, 3, and 6 months after injectior
ures in Rheumatology–Osteoarthritis Research Society International (OMERACT-
response. A repeated measures analysis of variance was used for comparison

Results: No major complications occurred in either group. The SVF group had a
2%) and minor complications related to the fat harvest site (SVF 34%, ASC 5%).
and KOOS domains. Specifically, in the ASC group, symptoms improved earlier
to a greater degree (55%; $P < .05$) compared with the SVF group (44%). The pr
ASC group was slightly higher (ASCs, 61%; SVF, 55%; $P = .25$).

Conclusion: It was observed that both ASCs and SVF resulted in clinical improvement in patients with knee OA, but that ASCs outperform SVF in the early reduction of symptoms and pain with less comorbidity.

Level III Cohort Clinical Trial

Cultured adipose-derived stem cells and non-cultured SVF

- 80 patients, Grade 2–4 knee OA
  - 42 patients (59 knees) received 1.28 × 107 ADSCs,
  - 38 patients (69 knees) received a 5 mL SVF injection.
- VAS pain score and KOOS up to 6 months were evaluated.

The American Journal of Sports Medicine

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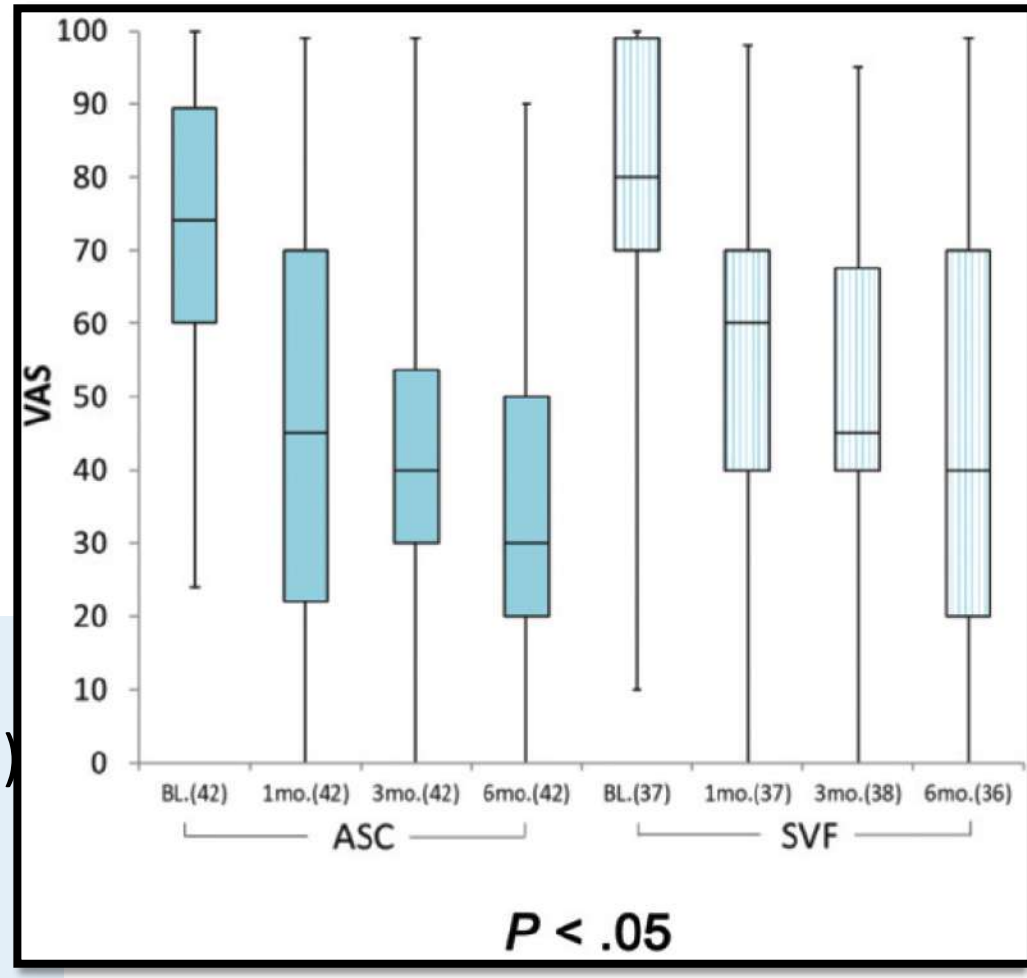
Masaki Otsuji,* MD, Stephen Lyman,‡ PhD, Kazunori Shimomura,§ MD, PhD,

- SVFs had a higher frequency of knee effusion (8% vs.%2) and harvest site complications (34% vs. 5%).
- In the ADSC treated group, pain VAS and KOOS domains improved by 3 months, and pain VAS decreased by 55% compared to the SVF group (44%).



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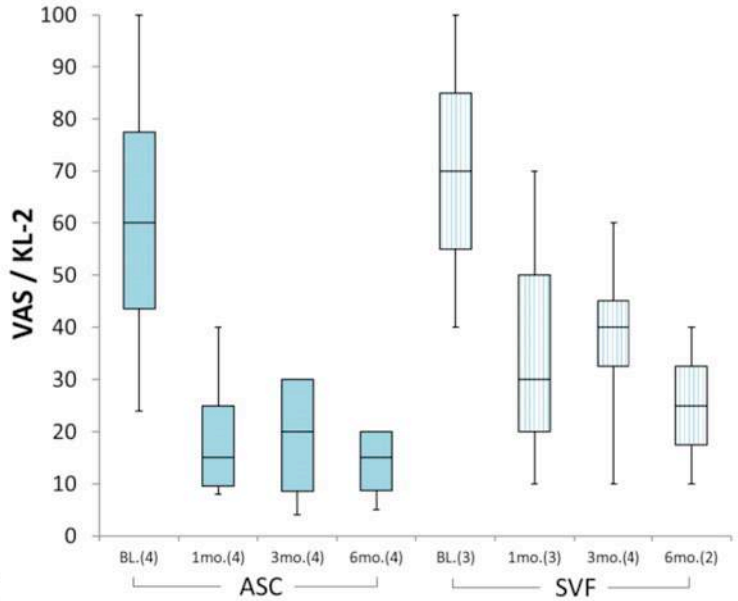
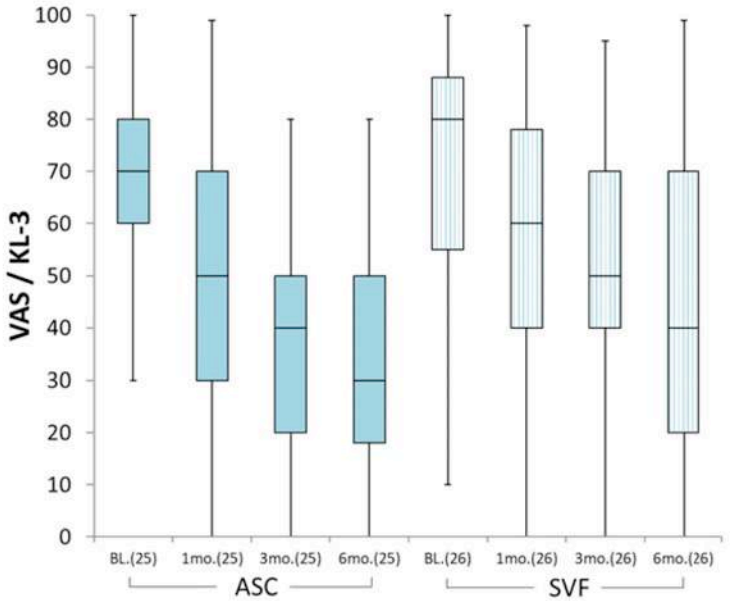
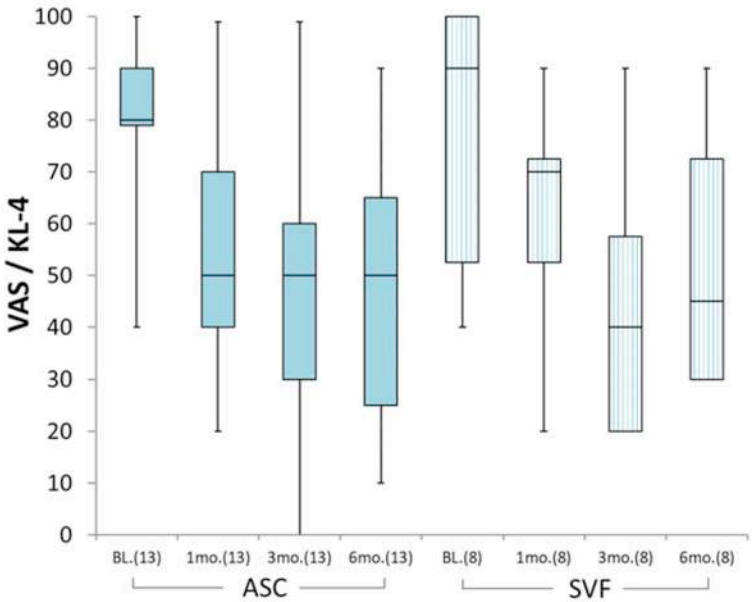
- Both groups resulted in clinical improvement;
  - ADSCs outperformed SVF in the early reduction of symptoms and pain with few complications.







Mean improvement rate(%) ±SD	77.6±4.2	58.9±22.7	55.6±21.3	43.9±25.6	43.5±21.4	38.1±19.3

Clinical Efficacy of Intra-articular Mesenchymal Stromal Cells for the Treatment of Knee Osteoarthritis

A Double-Blinded Prospective Randomized Controlled Clinical Trial

Jaime R. Garza,* MD, Richard E. Campl

The American Journal of Sports Medicine

- **Double-Blinded Randomized Study**
- **Intra-Articular Injection of SVF for Knee OA Treatment**

Background: Currently, there are limited nonc
apies have emerged as promising treatments
efficient medium for intra-articular administrat

Hypothesis: Patients receiving intra-articular S
injections, and this improvement would be dose dependent.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: This was a multisite prospective double-blinded randomized placebo-controlled clinical trial. Adult patients with symptomatic knee OA were eligible. Thirty-nine patients were randomized to high-dose SVF, low-dose SVF, or placebo (1:1:1). SVF was obtained via liposuction, processed to create the cellular implant, and injected during the same clinical visit. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and magnetic resonance images were obtained preoperatively and at 6 and 12 months after injection. The Wilcoxon rank sum nonparametric test was utilized to assess statistical significance, and the Hodges-Lehmann location shift was used to assess superiority.

Results: The median percentage change in WOMAC score at 6 months after injection for the high-dose, low-dose, and placebo groups was 83.9%, 51.5%, and 25.0%, respectively. The high- and low-dose groups had statistically significant changes in WOMAC scores when compared with the placebo group (high dose, $P = .04$; low dose, $P = .02$). The improvements were dose dependent. The median percentage change in WOMAC score from baseline to 1 year after injection for the high-dose, low-dose, and placebo groups was 89.5%, 68.2%, and 0%, respectively. The high- and low-dose groups displayed a greater percentage change at 12 months when compared with the placebo group (high dose, $P = .006$; low dose, $P = .009$). Magnetic resonance image review revealed no changes in cartilage thickness after treatment. No serious adverse events were reported.

Conclusion: Intra-articular SVF injections can significantly decrease knee OA symptoms and pain for at least 12 months. The efficacy and safety demonstrated in this placebo-controlled trial support its implementation as a treatment option for symptomatic knee OA.

Registration: NCT02726945 (ClinicalTrials.gov identifier)

Clinical Efficacy of Intra-articular Mesenchymal Stromal Cells for the Treatment of Knee Osteoarthritis

A Double-Blinded Prospective Randomized Controlled Clinical Trial

Jaime R. Garza,* MD, Richard E. Campbell,† BS, Fotios

The American Journal of Sports Medicine

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- 39 patients,
- 40 -75 years old with symptomatic knee OA

- <u>Treatment groups;</u>
  - high-dose SVF (3.0 × 107 cells),
  - low-dose SVF (1.5 × 107 cells),
  - placebo group (zero cells).

Clinical Efficacy of Intra-artic Mesenchymal Stromal Cells for the Treatment of Knee Os

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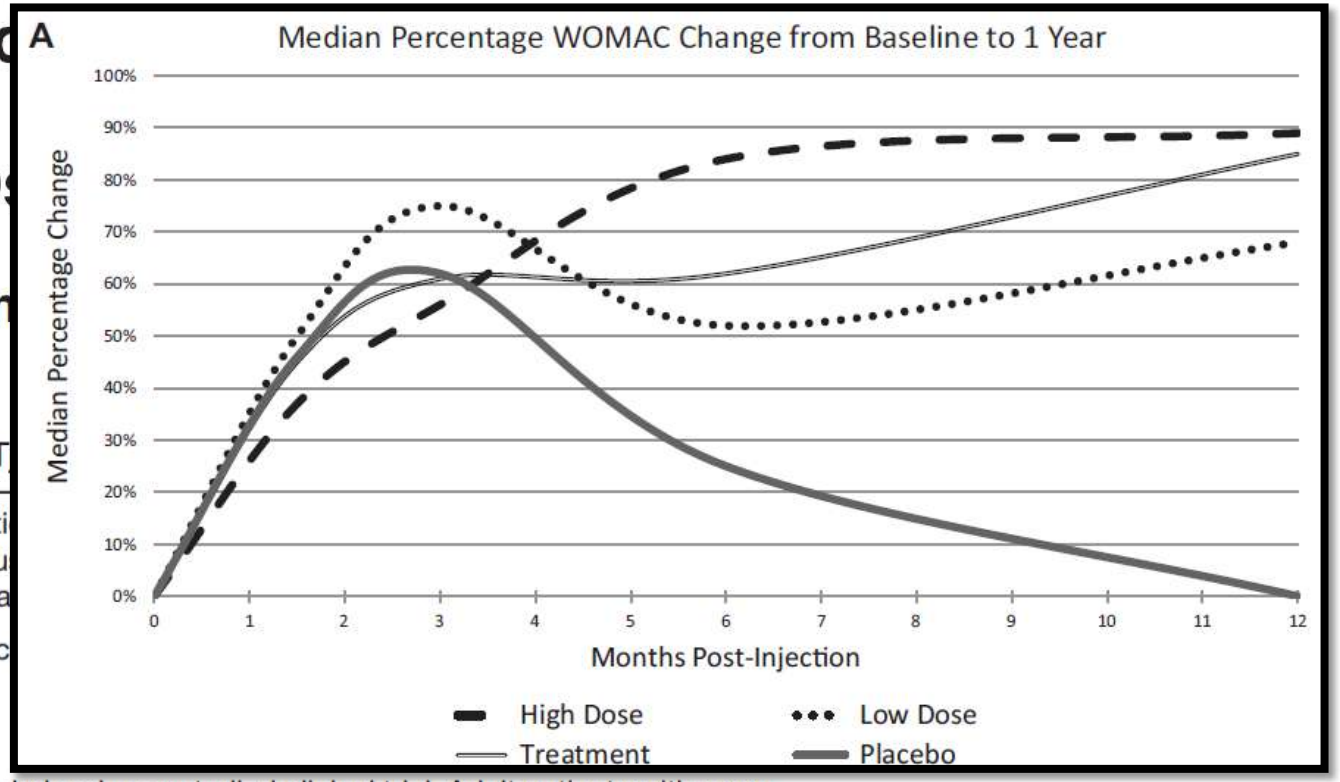

High-dose

Low-dose

Placebo

WOMAC Median Percentage Changes

	6 Months	12 Months
High-dose group	83.9%	89,5%
Low-dose group	51.5%	68,2%
Plasebo	25.0%	0%

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Study Design: Randomized controlled trial; Level of evidence, 1.

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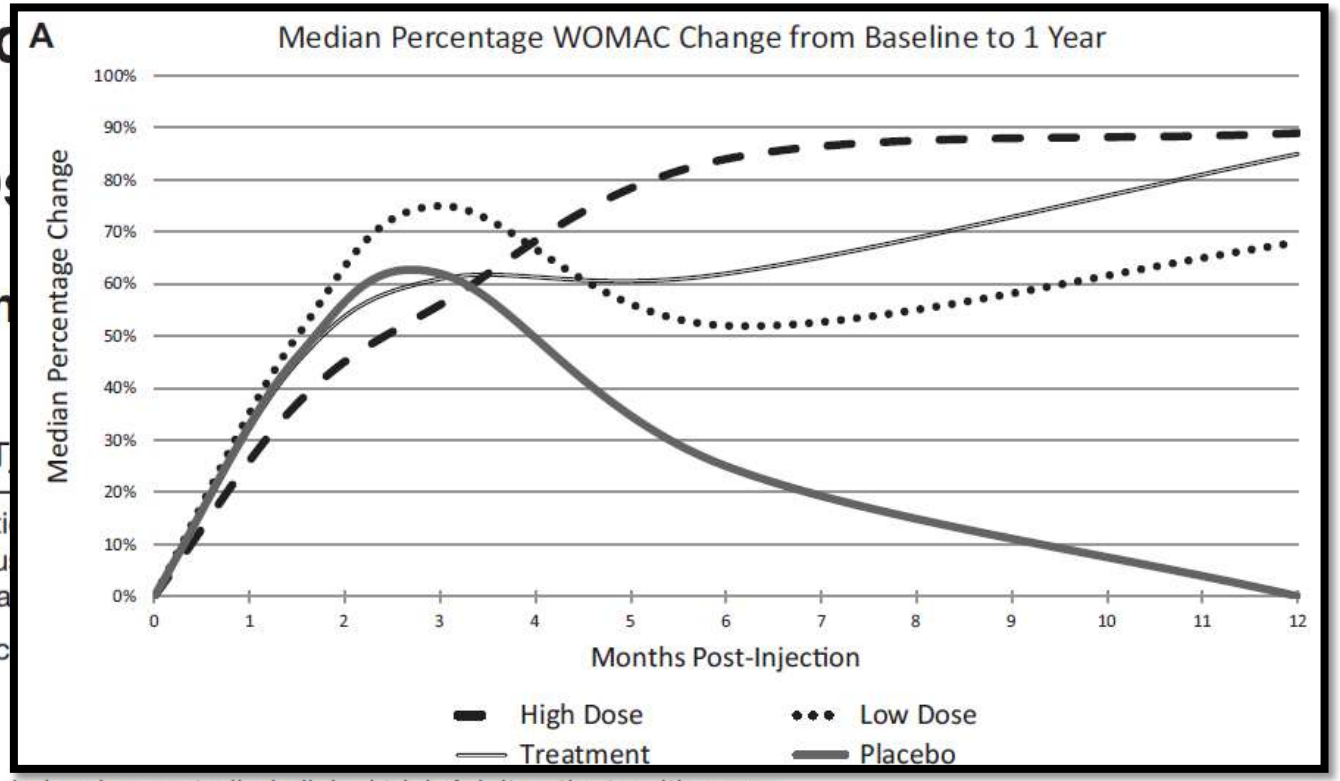
Results: The median percentage change in WOMAC score at 6 months after injection for the high-dose, low-dose, and placebo groups was 83.9%, 51.5%, and 25.0%, respectively. The high- a WOMAC scores when compared with the placebo group (high c dose dependent. The median percentage change in WOMAC sc low-dose, and placebo groups was 89.5%, 68.2%, and 0%, resp percentage change at 12 months when compared with the placebo group (high dose, $P = .006$; low dose, $P = .009$). Magnetic resonance image review revealed no changes in cartilage thickness after treatment. No serious adverse events were reported.

Conclusion: Intra-articular SVF injections can significantly decrease knee OA symptoms and pain for at least 12 months. The efficacy and safety demonstrated in this placebo-controlled trial support its implementation as a treatment option for symptomatic knee OA.

Registration: NCT02726945 (ClinicalTrials.gov identifier)



High-dose

Low-dose

Placebo

- The **high- and low-dose groups** had statistically significant changes compared with the placebo group.
- The improvements were dose-dependent.

Global Surgery

Research Article ISSN: 2056-7863

Stromal vascular fraction cells of adipose and connective tissue in people with osteoarthritis: A case control prospective multi-centric non-randomized study

Jaroslav Michalek[1,11]*, Rene Moster[2], Ladislav Lukac[3], Kenneth Proefrock[4], Miron Petrasovic rinskas[7], Jaroslav Michalek[8], Jan Kristek[9], Jan Travnik[10], Petr Jabandziev[11], Marek Cibulka[1], Jo Dudasova[1]

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[2]Revmacenter, Brno, Czech Republic
[3]ArthroBiotherapy, Ostrava, Czech Republic
[4]Stem Cell Center, Phoenix, AZ, USA
[5]Medissimo Hospital, Bratislava, Slovakia
[6]First Surgery, Pardubice, Czech Republic
[7]Department of Pharmacology, Lithuanian University of Health Sciences, Kaunas, Lithuania
[8]Department of Econometrics, University of Defense, Brno, Czech Republic
[9]Department of Radiology, Surgal Clinic, Brno, Czech Republic
[10]Department of Orthopedics, Traumatology Hospital, Brno, Czech Republic
[11]Department of Pediatrics, University Hospital Brno, Brno, Czech Republic

Abstract

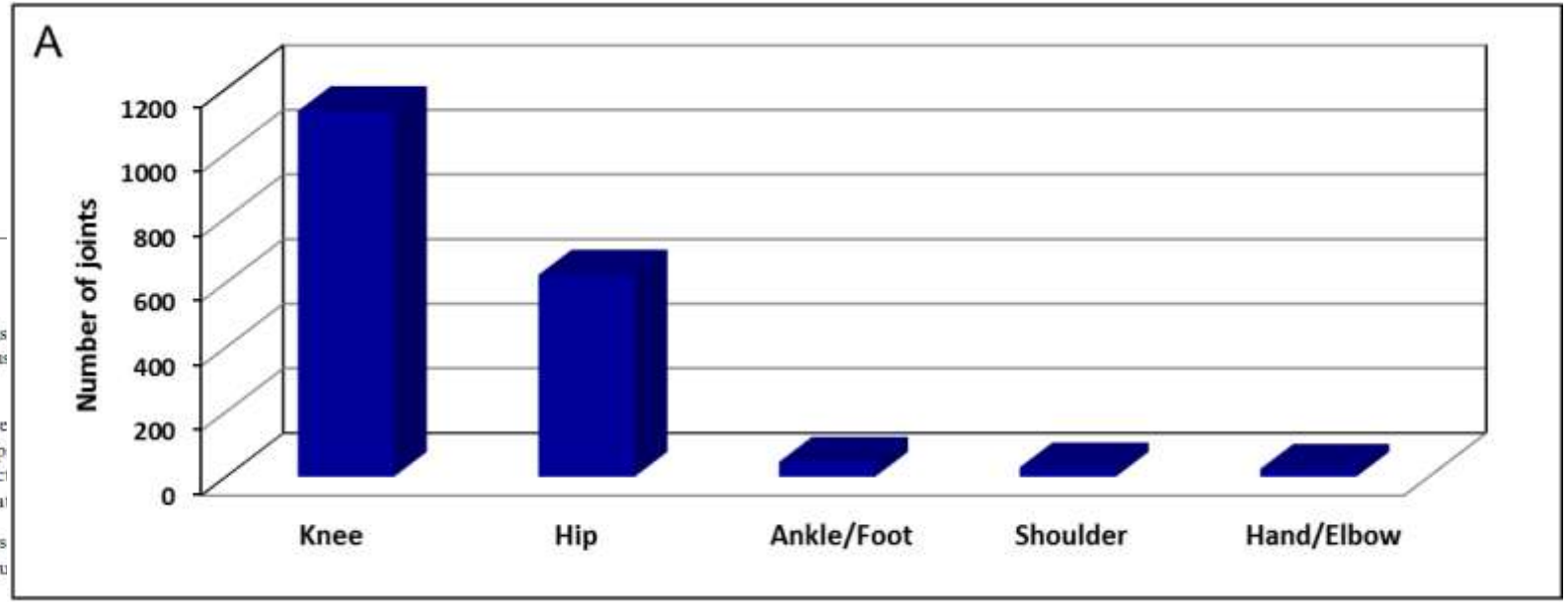
Objective: Stromal vascular fraction (SVF), containing high amount of stem cells and other regenerative cells that is associated with adipose tissue. Here we evaluated safety and clinical efficacy of freshly isolated autologous non-randomized study in patients with grade 2-4 degenerative osteoarthritis.

Methods: A total of 1128 patients underwent standard liposuction under local anesthesia and SVF cells were joints. A total of 1856 joints, mainly knee and hip joints, were treated with a single dose of SVF cells. 1114 p 17.2 months) for safety and efficacy. Modified KOOS/HOOS Clinical Score was used to evaluate clinical effec limping, extent of joint movement, and joint stiffness evaluation before and at 3,6 and 12 months after the trea

Results: No serious side effects, systemic infection or cancer was associated with SVF cell therapy. Most patients At least 75% Score improvement was noticed in 63% of patients and at least 50% Score improvement was docu therapy. Obesity and higher grade of OA were associated with slower healing.

Conclusion: Here we report a novel and promising treatment approach for patients with degenerative osteoarthritis that is safe, cost-effective, and relying only on autologous cells.

- Large case-controlled, multi-centric non-randomized trial
- 1128 patients, a total of 1856 joints.



Global Surgery

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Research Article ISSN: 2056-7863

Stromal vascular fraction cells of adipose and connective tissue in people with osteoarthritis: A case control prospective multi-centric non-randomized study

- Safety and clinical efficacy of SVFs in patients with grade 2–4 OA.

[6]First Surgery, Pardubice, Czech Republic
[7]Department of Pharmacology, Lithuanian University of Health Sciences, Kaunas, Lithuania
[8]Department of Econometrics, University of Defense, Brno, Czech Republic
[9]Department of Radiology, Surgal Clinic, Brno, Czech Republic
[10]Department of Orthopedics, Traumatology Hospital, Brno, Czech Republic
[11]Department of Pediatrics, University Hospital Brno, Brno, Czech Republic

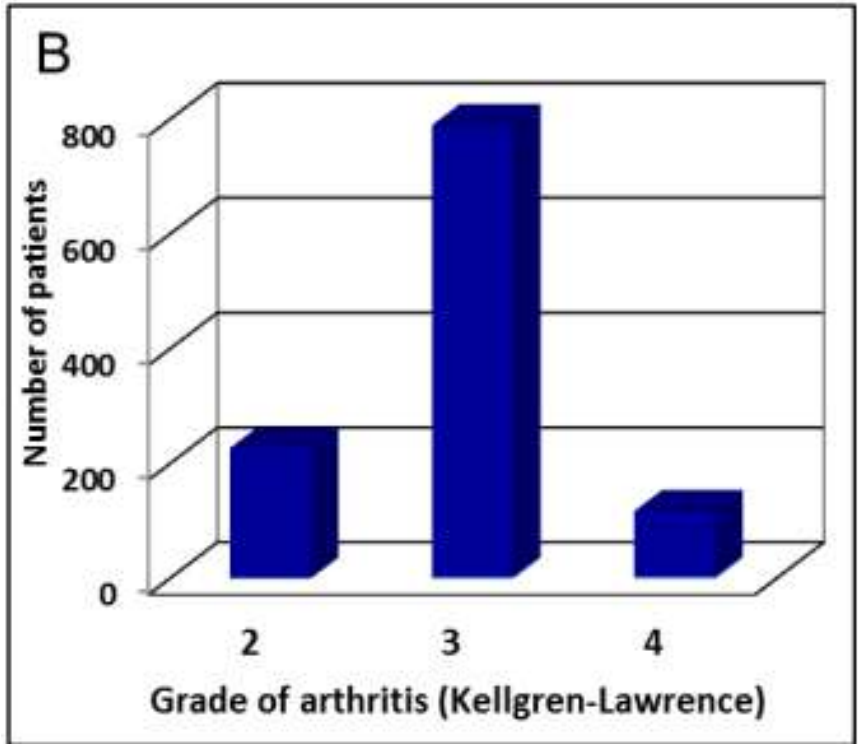
Abstract

Objective: Stromal vascular fraction (SVF), containing high amount of stem cells and other regenerative cells, can be easily obtained from loose connective tissue that is associated with adipose tissue. Here we evaluated safety and clinical efficacy of freshly isolated autologous SVF cells in a case control prospective multi-centric non-randomized study in patients with grade 2-4 degenerative osteoarthritis.

Methods: A total of 1128 patients underwent standard liposuction under local anesthesia and SVF cells were isolated and prepared for application into 1-4 large joints. A total of 1856 joints, mainly knee and hip joints, were treated with a single dose of SVF cells. 1114 patients were followed for 12.1-54.3 months (median 17.2 months) for safety and efficacy. Modified KOOS/HOOS Clinical Score was used to evaluate clinical effect and was based on pain, non-steroid analgesic usage, limping, extent of joint movement, and joint stiffness evaluation before and at 3,6 and 12 months after the treatment.

Results: No serious side effects, systemic infection or cancer was associated with SVF cell therapy. Most patients gradually improved 3-12 months after the treatment. At least 75% Score improvement was noticed in 63% of patients and at least 50% Score improvement was documented in 91% of patients 12 months after SVF cell therapy. Obesity and higher grade of OA were associated with slower healing.

Conclusion: Here we report a novel and promising treatment approach for patients with degenerative osteoarthritis that is safe, cost-effective, and relying only on autologous cells.



Global Surgery

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Research Article ISSN: 2056-7863

Stromal vascular fraction cells of adipose and connective tissue in people with osteoarthritis: A case control prospective multi-centric non-randomized study

**Jaroslav Michalek[1,11]*, Rene Moster[2], Ladislav Lukac[3], Kenn
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[2]Revmacenter, Brno, Czech Republic
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Conclusion: Here we report a novel and promising treatment approach for patients with degenerative osteoarthritis that is safe, cost-effective, and relying only on autologous cells.

- Single dose intra-articular or peri-articular injection.
- Follow-up ---> up to 54 months
- Modified KOOS/HOOS Clinical Score was used for assessments 12 months post-treatment

Global Surgery

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Research Article ISSN: 2056-7863

Stromal vascular fraction cells of adipose and connective tissue in people with osteoarthritis: A case control prospective multi-centric non-randomized study

Jaroslav Michalek[1,11]*, Rene Moster[2], Ladislav Lukac[3], Kenneth Proefrock[4], Miron Petrasovic[5], Jakub Rybar[5], Ales Chaloupka[6], Adas Darinskas[7], Jaroslav Michalek[8], Jan Kristek[9], Jan Travnik[10], Petr Jabandziev[11], Marek Cibulka[1], Josef Skopalik[1], Zlatuse Kristkova[1] and Zuzana Dudasova[1]

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Conclusion: Here we report a novel and promising treatment approach for pat
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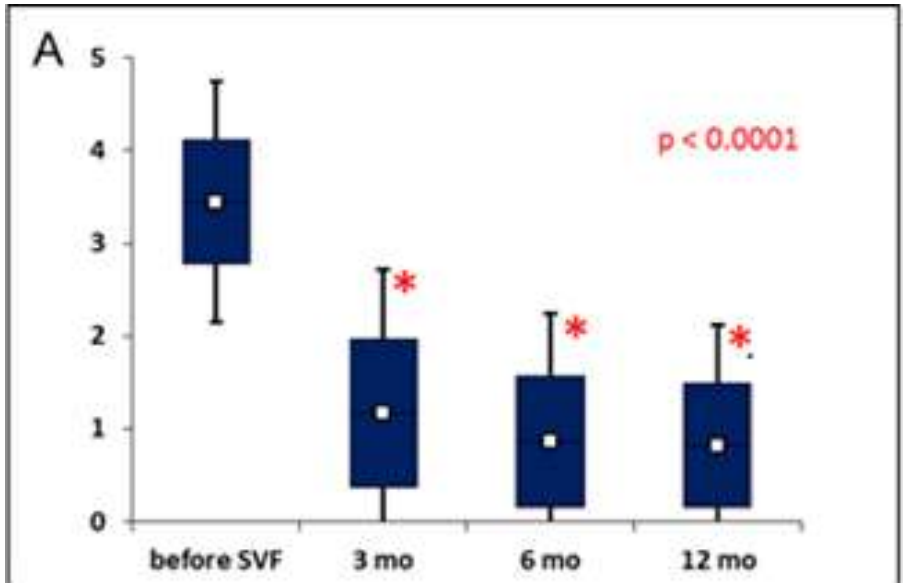

- No serious side effects.
- <u>At 12 months;</u>
  - 75% improvement was recorded in 63% of the patients,
  - 50% improvement in 91% of the patients.
- Indicates that autologous SVF for OA is safe and clinically effective.

International Orthopaedics

International Orthopaedics
https://doi.org/10.1007/s00264-018-4099-0

ORIGINAL PAPER

Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a double-blind randomized self-controlled trial

Zheping Hong[1] · Jihang Chen[2] · Shuijun Zhang[2] · Chen Zhao[2] · Minggu

Abstract

Objective The purpose of this study was to compare the clinical and radiological efficac
vascular fraction (SVF) versus hyaluronic acid in patients with bilateral knee osteoarth

Methods Sixteen patients with bilateral symptomatic knee osteoarthritis (K-L grade II to I
on a ten-point VAS score) were enrolled in this study, which were randomized into two groups. Each patient received 4-ml
autologous adipose-derived SVF treatment (group test, $n = 16$) in one side of knee join
acid treatment (group control, $n = 16$) in the other side. The clinical evaluations we
operatively at one month, three months, six months, and 12-months follow-up visit,
(VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
The whole-organ assessment of the knees was performed with whole-organ magnetic reson
MRI at baseline, six months and 12-months follow-up. The articular repair tissue was ass
magnetic resonance observation of cartilage repair tissue (MOCART) score based on follo

Results No significant baseline differences were found between two groups. Safety was
observed during 12-months follow-up. The SVF-treated knees showed significantly improvement in the mean VAS, WOMAC
scores, and ROM at 12-months follow-up visit compared with the baseline. In contrast, the mean VAS, WOMAC scores, and
ROM of the control group became even worse but not significant from baseline to
MOCART measurements revealed a significant improvement of articular cartilage repa
hyaluronic acid-treated knees.

Conclusion The results of this study suggest that autologous adipose-derived SVF treatment is safe and can effectively relief pain, improve function, and repair cartilage defects in patients with knee osteoarthritis.

- Double-blind randomized self-controlled trial

- 16 patients (32 knees)
- Bilateral knee OA (grade II–III) were randomized into two groups.

- <u>Single dose injection;</u>
- SVF ---> in one knee joint (test knee, n = 16).
- HA --> contralateral knee (control knee, n = 16).

- Follow-up at 1, 3, 6, and 12-months post-injection.

International Orthopaedics

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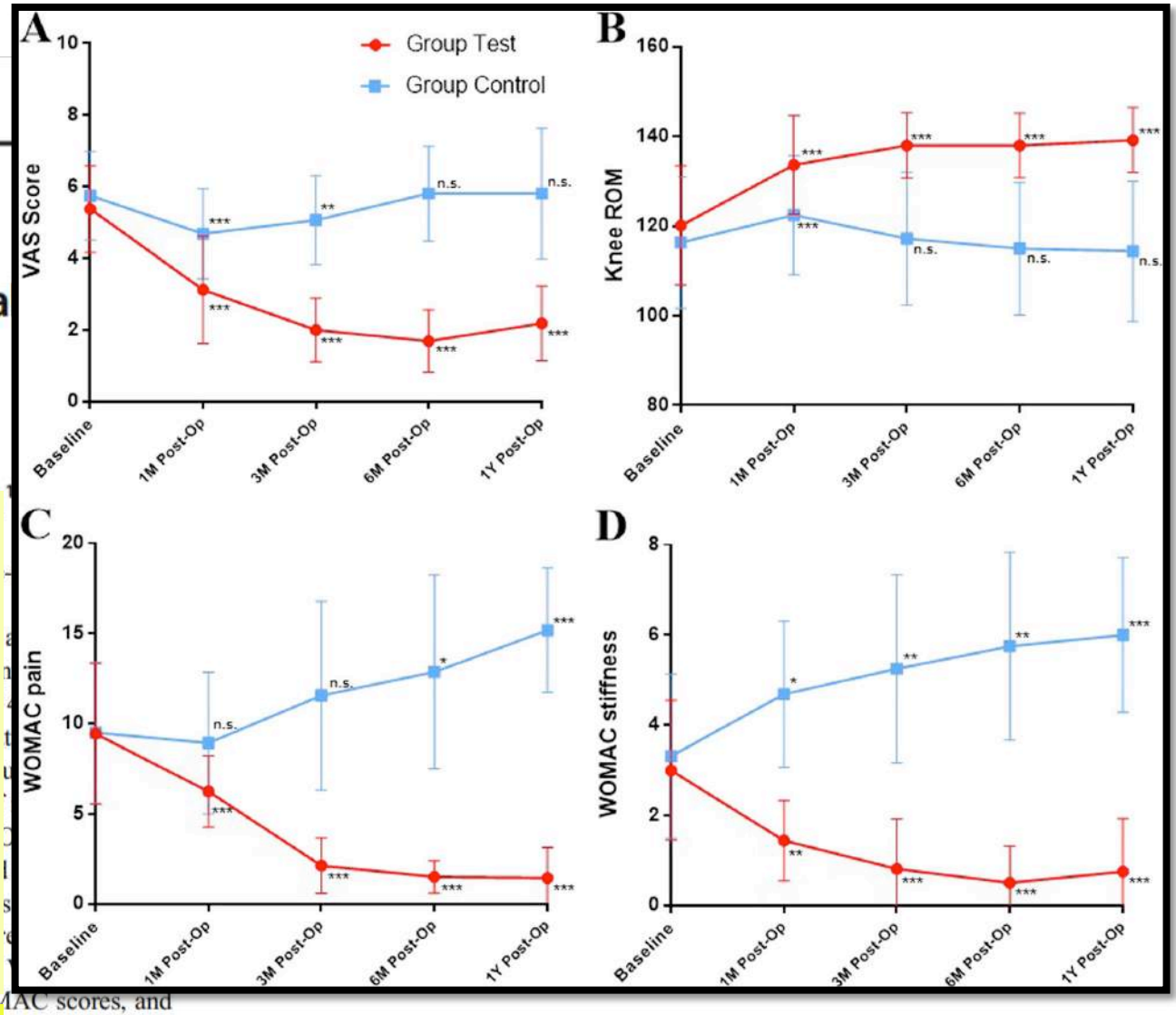
ORIGINAL PAPER

Intra-articular injection of autologous adipose-derived stroma fractions for knee osteoarthritis: a double-blind randomized self-controlled trial

- The SVF-treated knees showed significantly improved mean scores of;
- VAS,
- WOMAC, and
- range of motion (ROM) compared to baseline

- The HA group became worse.



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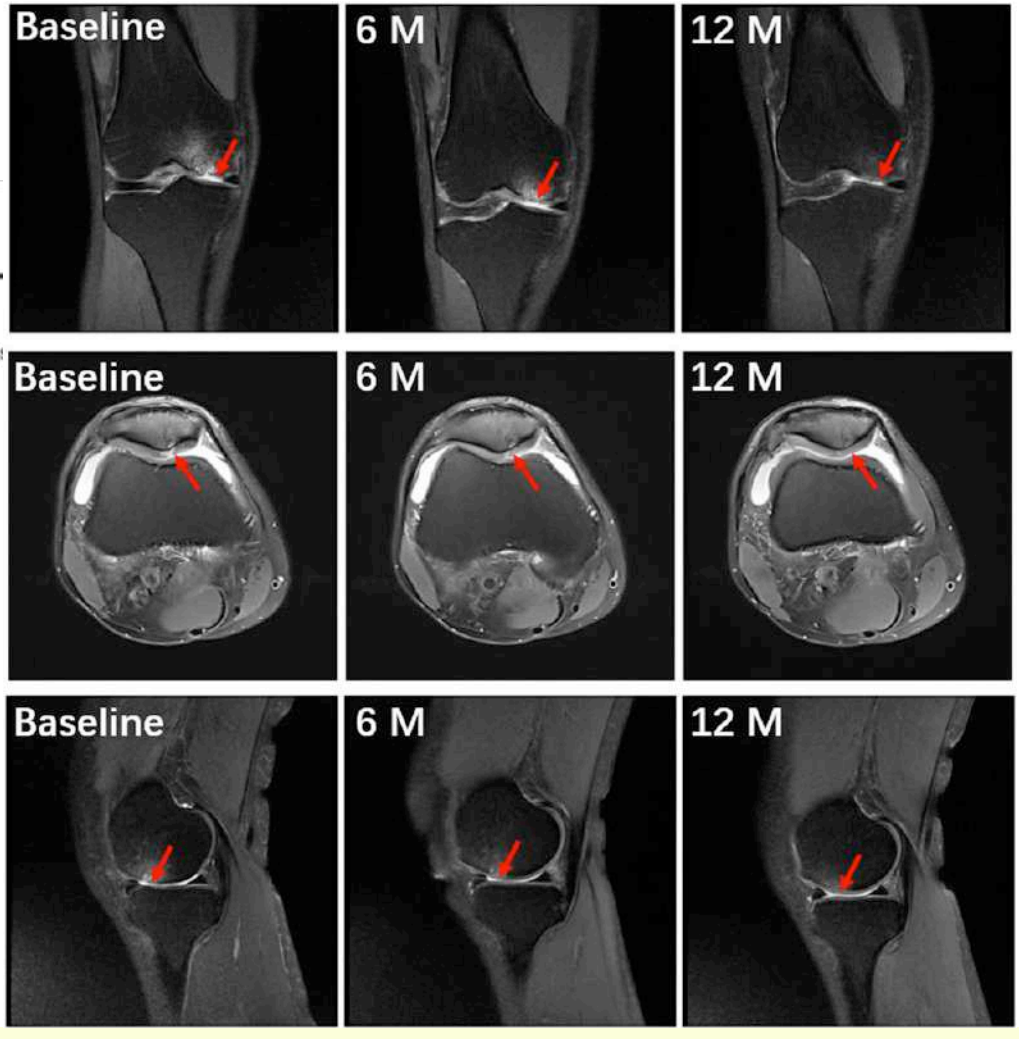
Zheping Hong[1] · Jihang Chen[2] · Shuijun Zhang[2] · Chen Zhao[2] · Mingguang Bi[2] · Xinji Chen[1] · Qing Bi[1,2]

Abstract

Objective The purpose of this study was to compare the clinical and radiological efficacy of autologous adipose-derived stromal vascular fraction (SVF) versus hyaluronic acid in patients with bilateral knee osteoarthritis.

Methods Sixteen patients with bilateral symptomatic knee osteoarthritis (K-L grade II to III; initial pain evaluated at four or greater on a ten-point VAS score) were enrolled in this study, which were randomized into two groups. Each patient received 4-ml autologous adipose-derived SVF treatment (group test, $n = 16$) in one side of knee joints and a single dose of 4-ml hyaluronic acid treatment (group control, $n = 16$) in the other side. The clinical evaluations were performed pre-operatively and post-operatively at one month, three months, six months, and 12-months follow-up visit, using the ten-point visual analog scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the knee range of motion (ROM).



- MRI measurements for cartilage repair (MOCART) revealed significant improvements in cartilage repair in SVF-treated knees.

- **Adipose-derived SVF can improve function and repair cartilage defects** of knee OA.

ISSN: 2469-570X

Berman et al. Int J Stem Cell Res Ther 2019, 6:064
DOI: 10.23937/2469-570X/1410064
Volume 6 | Issue 1
Open Access

International Journal of
Stem Cell Research & Therapy

ORIGINAL ARTICLE

Prospective Study of Autologous Adipose Derived Stromal Vascular Fraction Containing Stem Cells for the Treatment of Knee Osteoarthritis

Mark Berman, MD, Elliot Lander, MD, Thomas Grogan, MD, Walter O'Brien, MD, Jonathan Braslow, MD, Shawntae Dowell and Sean Berman, MS*

Cell Surgical Network, University of Southern California, USA

Background: The management of osteoarthritis of the knee runs the spectrum of care from a variety of conservative treatments often culminating in total joint arthroplasty. We initiated a large prospective study to evaluate whether autologous adipose derived stromal vascular fraction (SVF - rich in stem cells) therapy is a safe and effective option.

Methods: A patient funded prospective study of 2,586 patients from a network of physicians participated in an IRB approved study using autologous stromal vascular fraction SVF (ClinicalTrials.gov as NCT10953523). All patients were treated with a standardized surgical protocol to harvest lipoaspirate, isolate and deploy autologous SVF. Data was collected using an online registry and patients were followed-up via an automatic online database collection service.

Results: 2,586 patients were treated. Statistically significant improvement was seen at 1 and 2 years - meaning less pain and greater ease of mobility. There was no difference between male or female outcomes (82% overall improvement). All BMI levels showed improvements though higher BMIs had less improvement. There was no difference in outcomes between SVF alone or with PRP added to SVF. Improvement was the same regardless of payment or receiving free care. There were very few adverse events and those that did occur were largely very minor or easily treatable.

Conclusion: Deployment of autologous SVF represents a simple surgical procedure that can be safely performed in an adequate outpatient environment under straight local anesthesia and demonstrates very good outcomes even in difficult cases of chronic knee arthritis.

Multiple peer-reviewed publications exist showing that adipose derived stromal vascular fraction containing adult mesenchymal stem cells may improve the condition of inflammatory knee conditions [1-5].

Animal studies show double-blind examples of significant improvements in using adipose derived stem cells for degeneration and injuries [6].

Multiple studies suggest that allogeneic stem cells may be efficacious and safe [7-11]. While an off-the-shelf stem cell product might be idyllic, there are still long-term concerns about immunogenicity as allogeneic cells, while initially immune neutral, or immune evasive, will differentiate into the donor immune characteristics [12,13]. Autologous stem cells possess no risk of short or long-term allergic or immune response. Additionally, an allogeneic source of human stem cells must be free of any infectious agents. As humans are not grown in sterile environments, it's virtually impossible to assure society that allogeneic sources are devoid of possible prions or viruses that may go undetected. A variety of papers have already documented risks of disease transmission from a variety of allogeneic sources [14-18].

Patients presenting with painful knee osteoarthritis may benefit from receiving immediate point of care ad-

Large-scale prospective study

- 2586 participants,
- SVF was injected into the affected knee or knees.
- Platelet-rich plasma (PRP) was added in some cases.
- Visual acuity pain score of 0 (no pain) -10 (worse pain) for (1) at rest, (2) standing, (3) walking, and (4) running.

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ORIGINAL ARTICLE

Prospective Study of Autologous Adipos Vascular Fraction Containing Stem Cells of Knee Osteoarthritis

Mark Berman, MD, Elliot Lander, MD, Thomas Grogan, MD, Walte Jonathan Braslow, MD, Shawntae Dowell and Sean Berman, MS*

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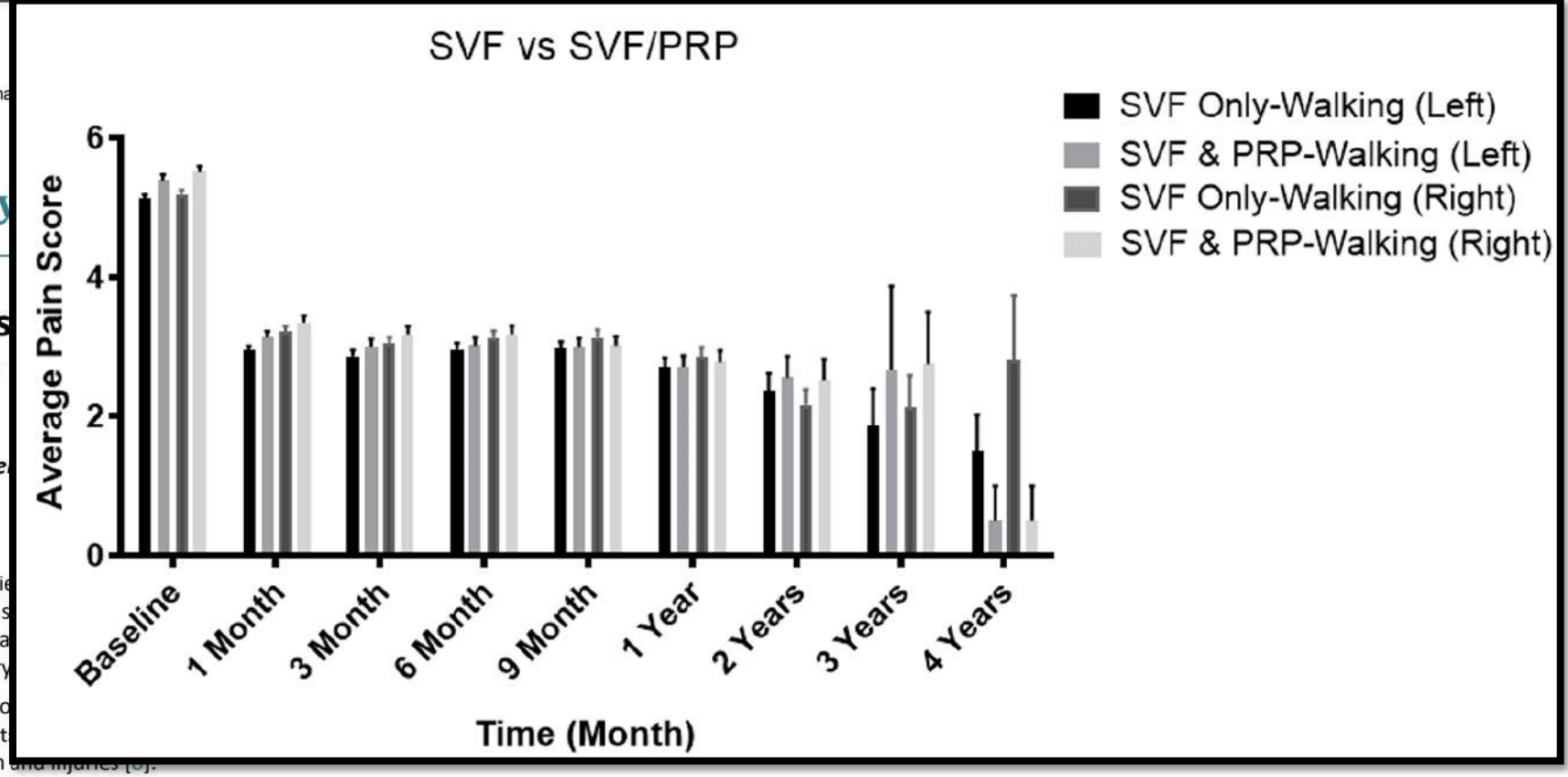

- Overall 82% improvement by autologous SVF application.
- Statistically significant functional recoveries from pain and mobility within 1 to 2 years.
- No gender differences in outcomes.
- No difference between SVF alone and SVF+PRP.

Journal of Clinical Orthopaedics and Trauma 10 (2019) 76–80

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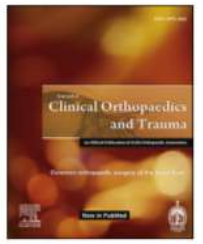

Stromal vascular fraction cell therapy for osteoarthritis in elderly: Multicenter case-control study

Jaroslav Michalek [a, b, c], Alena Vrablikova [b, *], Adas Darinskas [a, d], Ladislav Lukac [e], Jaroslav Prucha [f], Josef Skopalik [b, g], Jan Travnik [b, h], Marek Cibulka [b], Zuzana Dudasova [a, b]

- **Long-Term Study**
- Efficacy of SVF for knee OA

- 29 patients, between 80-94 years old.
  - ~10% of the patients were at grade 2,
  - ~ 50% with grade 3, and
  - ~ 40% with grade 4 degenerations.

Journal of Clinical Orthopaedics and Trauma 10 (2019) 7

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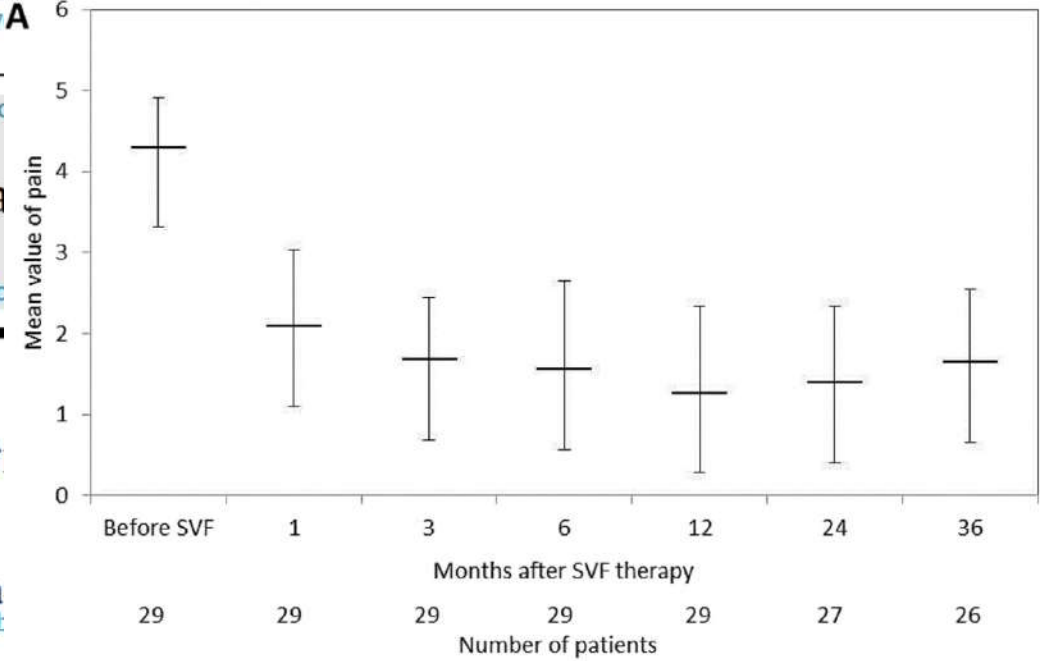
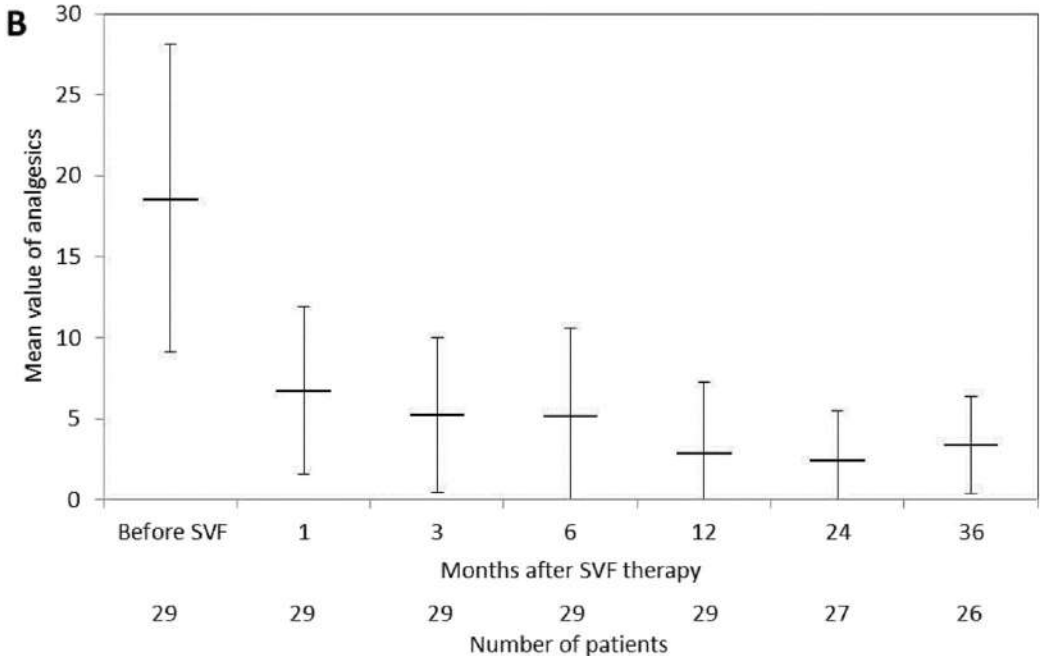


- Pain score, number of analgesics/NSAIDs per week were significantly decreased from the first-month to 36 months post-SVF therapy.



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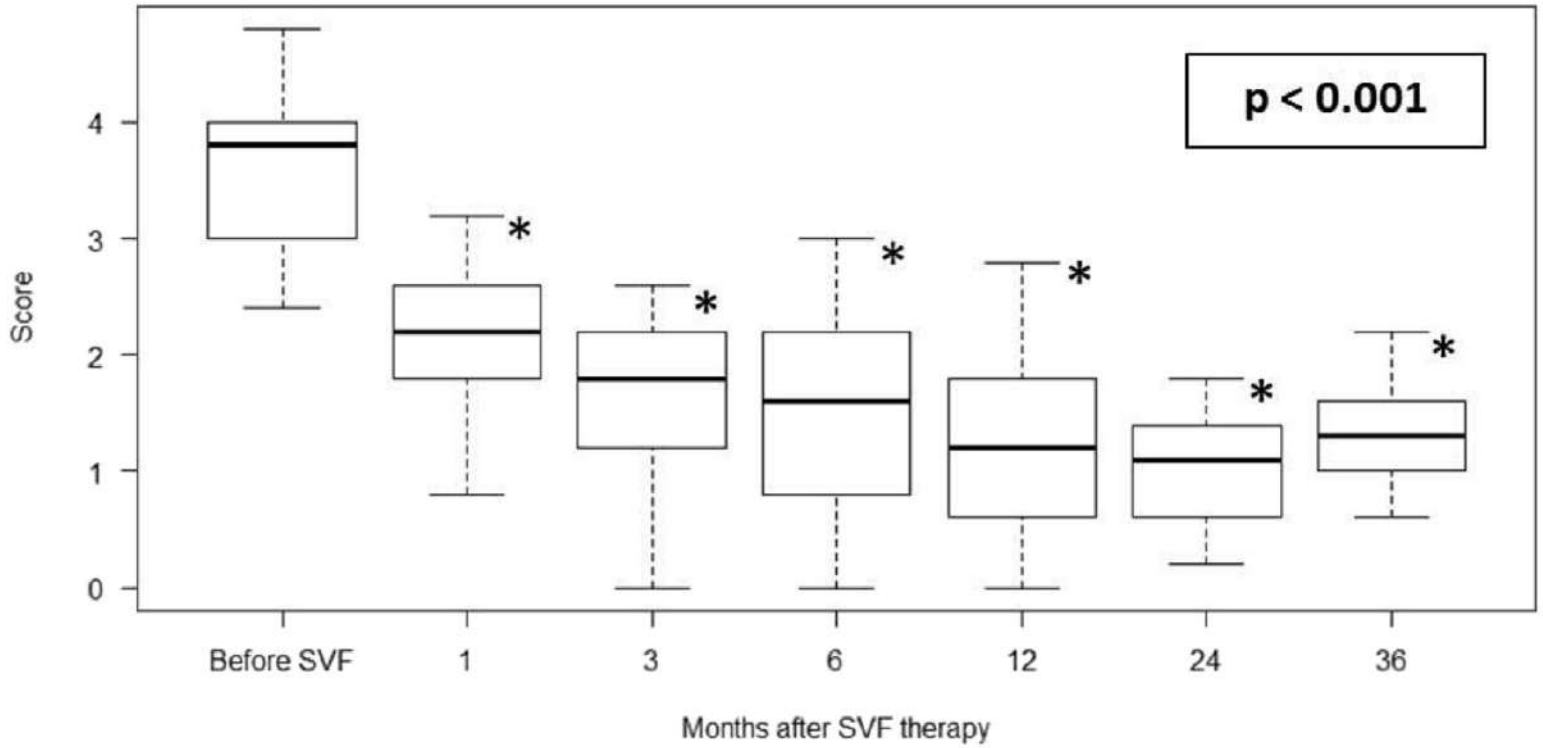

- Similar results were obtained on limping, joint movement, and stiffness.
- SVF represents an important tool in the regeneration of joints in elderly patients.

International Orthopaedics
https://doi.org/10.1007/s00264-018-4192-4

ORIGINAL PAPER

International Orthopaedics

Concentrated adipose tissue infusion for the treatment of knee osteoarthritis: clinical and histological observations

Ilaria Roato[1] · Dimas Carolina Belisario[1] · Mara Compagno[1] · Aurora Lena[2] ·
Federico Mussano[4] · Tullio Genova[5] · Laura Godio[6] · Giuseppe Perale[7,8] · Matt
Carlotta Castagnoli[9] · Tiziana Robba[10] · Lamberto Felli[3] · Riccardo Ferracini[3]

Received: 23 July 2018 / Accepted: 27 September 2018

- MAT-SVFs were injected to the knees of 20 patients.

Abstract

Purpose Osteoarthritis (OA) is characterized by articular cartilage degeneration and subchondral bone sclerosis. OA can benefit of non-surgical treatments with collagenase-isolated stromal vascular fraction (SVF) or cultured-expanded mesenchymal stem cells (ASCs). To avoid high manipulation of the lipoaspirate needed to obtain ASCs and SVF, we investigated whether articular infusions of autologous concentrated adipose tissue are an effective treatment for knee OA patients.

Methods The knee of 20 OA patients was intra-articularly injected with autologous concentrated adipose tissue, obtained after centrifugation of lipoaspirate. Patients' articular functionality and pain were evaluated by VAS and WOMAC scores at three, six and 18 months from infusion. The osteogenic and chondrogenic ability of ASCs contained in the injected adipose tissue was studied in in vitro primary osteoblast and chondrocyte cell cultures, also plated on 3D-bone scaffold. Knee articular biopsies of patients previously treated with adipose tissue were analyzed. Immunohistochemistry (IHC) and scanning electron microscopy (SEM) were performed to detect cell differentiation and tissue regeneration.

Results The treatment resulted safe, and all patients reported an improvement in terms of pain reduction and increase of function. According to the osteogenic or chondrogenic stimulation, ASCs expressed alkaline phosphatase or aggrecan, respectively. The presence of a layer of newly formed tissue was visualized by IHC staining and SEM. The biopsy of previously treated knee joints showed new tissue formation, starting from the bone side of the osteochondral lesion.

Conclusions Overall our data indicate that adipose tissue infusion stimulates tissue regeneration and might be considered a safe treatment for knee OA.

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studied in in vitro primary osteoblast and chondrocyte c
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Results The treatment resulted safe, and all patients repor
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presence of a layer of newly formed tissue was visualized
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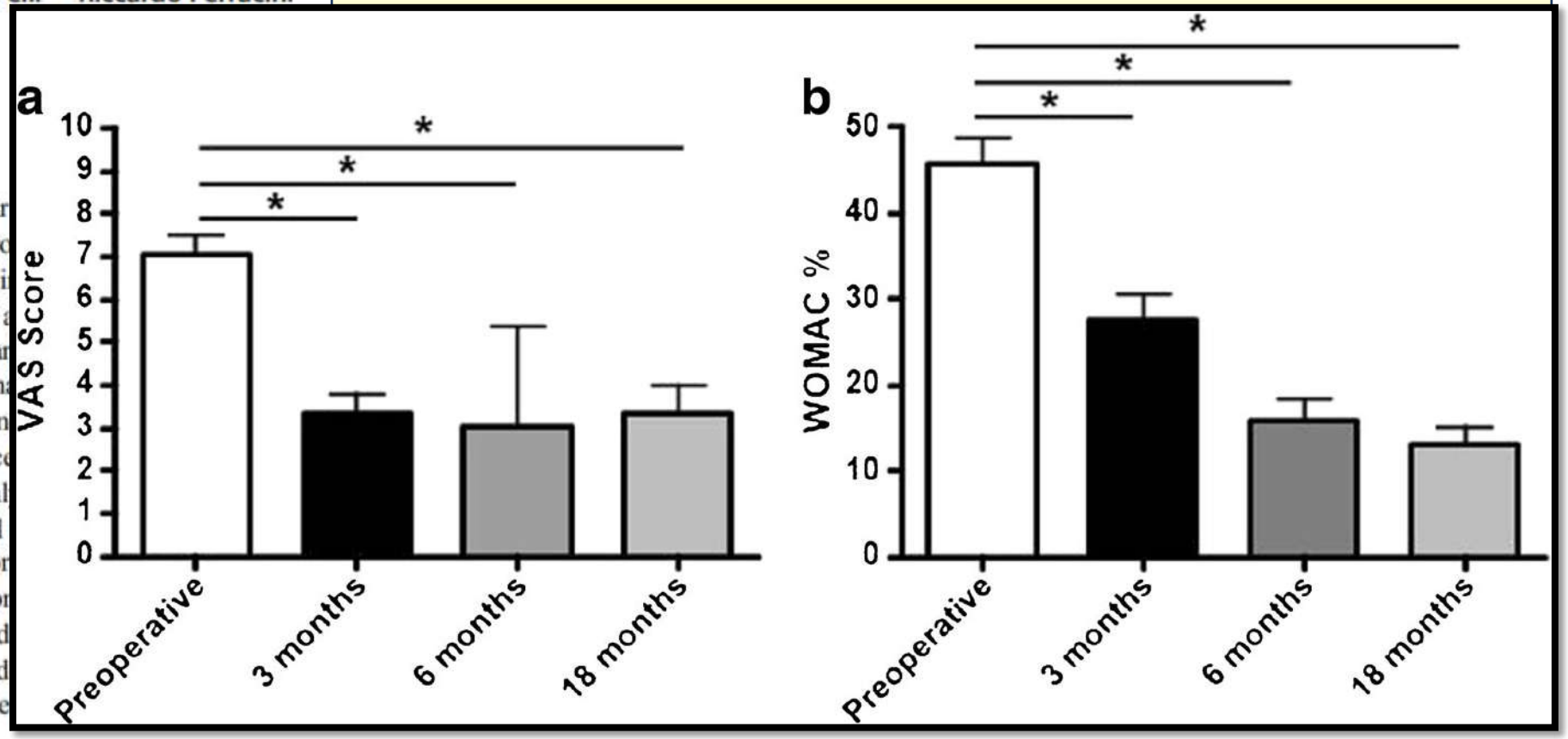
Conclusions Overall our data indicate that adipose tissue
treatment for knee OA.

- VAS and WOMAC scores 3–18 months post-injections. **All patients had improvement in pain and functional recovery.**



International Orthopaedics
https://doi.org/10.1007/s00264-018-4192-4

ORIGINAL PAPER

International Orthopaedics

Concentrated adipose tissue infusion for the treatment of knee osteoarthritis: clinical and histological observations

Ilaria Roato[1] · Dimas Carolina Belisario[1] · Mara Compagno[1] · Aurora Lena[2] ·
Federico Mussano[4] · Tullio Genova[5] · Laura Godio[6] · Giuseppe Perale[7,8] · Matt
Carlotta Castagnoli[9] · Tiziana Robba[10] · Lamberto Felli[3] · Riccardo Ferracini[3]

Received: 23 July 2018 / Accepted: 27 Septem

Abstract

Purpose Osteoarthritis (OA) is charac
of non-surgical treatments with collag
cells (ASCs). To avoid high manipula
infusions of autologous concentrated
Methods The knee of 20 OA patients
centrifugation of lipoaspirate. Patients
and 18 months from infusion. The os
studied in in vitro primary osteoblast
patients previously treated with adipo
(SEM) were performed to detect cell
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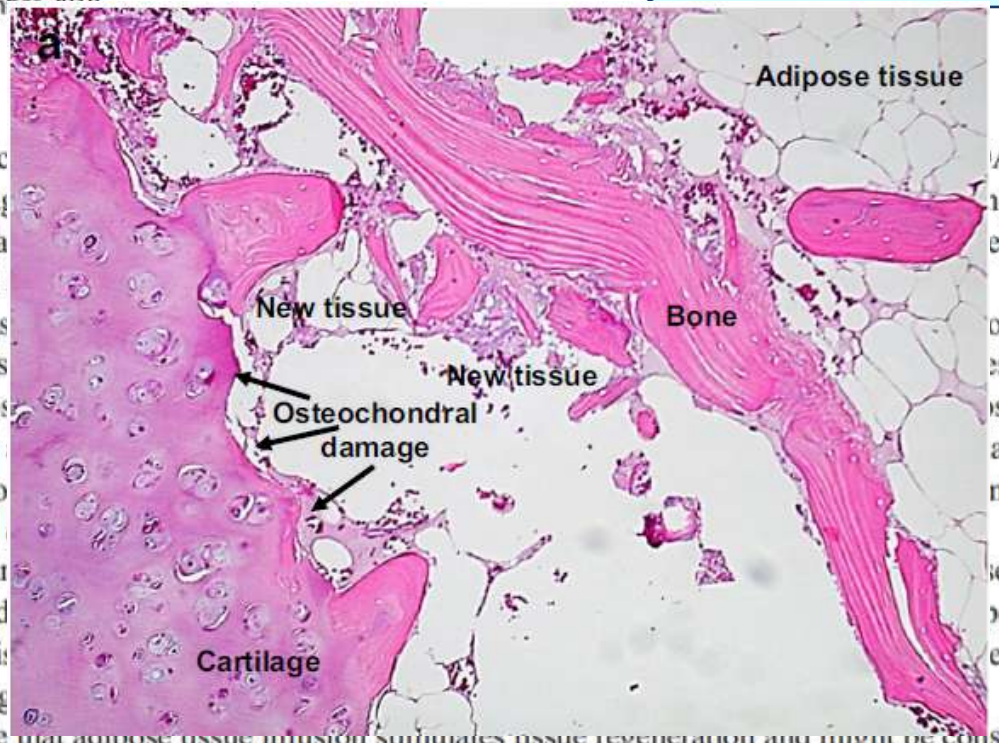
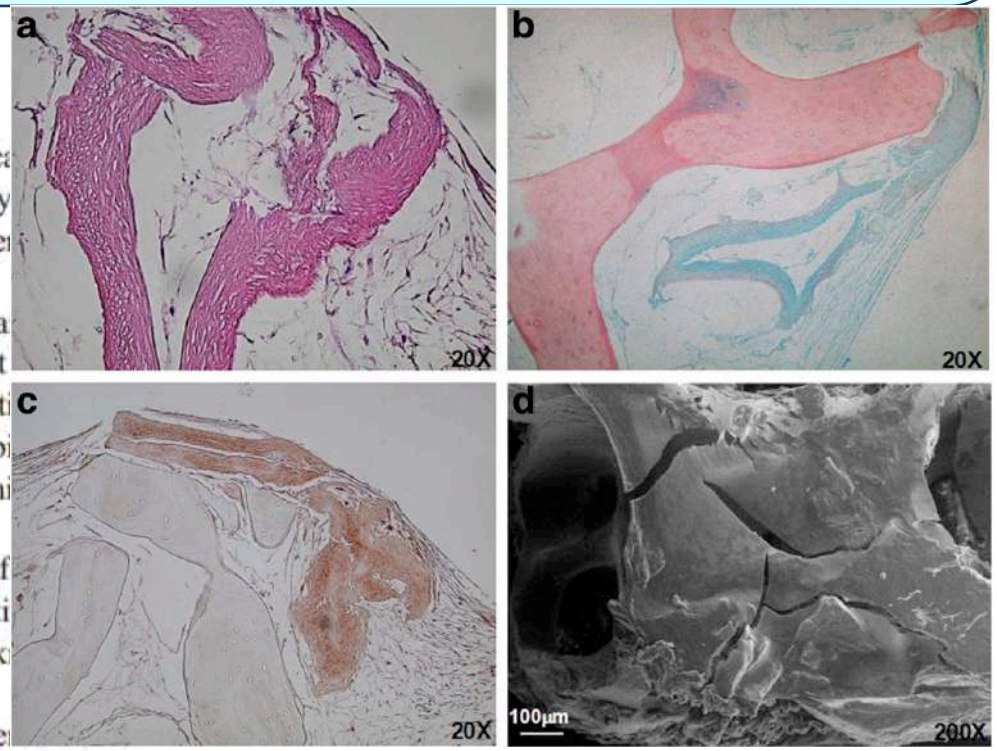
Conclusions Overall our data indicate
treatment for knee OA.

- Newly formed tissues were visualized by immunohistochemistry (IHC) staining and scanning electron microscope (SEM).





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Received: 23 July 2018 / Accepted: 27 September 2018

- MAT-SVFs are safe for knee OA and could stimulate tissue regeneration.

Abstract

Purpose Osteoarthritis (OA) is characterized by articular cartilage degeneration and subchondral bone sclerosis. OA can benefit of non-surgical treatments with collagenase-isolated stromal vascular fraction (SVF) or cultured-expanded mesenchymal stem cells (ASCs). To avoid high manipulation of the lipoaspirate needed to obtain ASCs and SVF, we investigated whether articular infusions of autologous concentrated adipose tissue are an effective treatment for knee OA patients.

Methods The knee of 20 OA patients was intra-articularly injected with autologous concentrated adipose tissue, obtained after centrifugation of lipoaspirate. Patients' articular functionality and pain were evaluated by VAS and WOMAC scores at three, six and 18 months from infusion. The osteogenic and chondrogenic ability of ASCs contained in the injected adipose tissue was studied in in vitro primary osteoblast and chondrocyte cell cultures, also plated on 3D-bone scaffold. Knee articular biopsies of patients previously treated with adipose tissue were analyzed. Immunohistochemistry (IHC) and scanning electron microscopy (SEM) were performed to detect cell differentiation and tissue regeneration.

Results The treatment resulted safe, and all patients reported an improvement in terms of pain reduction and increase of function. According to the osteogenic or chondrogenic stimulation, ASCs expressed alkaline phosphatase or aggrecan, respectively. The presence of a layer of newly formed tissue was visualized by IHC staining and SEM. The biopsy of previously treated knee joints showed new tissue formation, starting from the bone side of the osteochondral lesion.

Conclusions Overall our data indicate that adipose tissue infusion stimulates tissue regeneration and might be considered a safe treatment for knee OA.

11th ISABS CONFERENCE

Croat Med J. 2019;60:227-36
https://doi.org/10.3325/cmj.2019.60.227

CROATIAN MEDICAL JOURNAL

Early results of intra-articular micro-fragmented lipoaspirate treatment in patients with late stages knee osteoarthritis: a prospective study

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Split, Croatia

Aim To analyze clinical and functional effects of intra-articular injection of autologous micro-fragmented lipoaspirate (MLA) in patients with late stage knee osteoarthritis (KOA). Secondary aims included classifying cell types contributing to the treatment effect, performing detailed MRI-based classification of KOA, and elucidating the predictors for functional outcomes.

Methods This prospective, non-randomized study was conducted from June 2016 to February 2018 and enrolled 20 patients with late stage symptomatic KOA (Kellgren Lawrence grade III, n=4; and IV, n=16) who received an intra-articular injection of autologous MLA in the index knee joint. At baseline radiological KOA grade and MRI were assessed in order to classify the morphology of KOA changes. Stromal vascular fraction cells obtained from MLA samples were stained with antibodies specific for cell surface markers. Patients were evaluated at baseline and

- A prospective, non-randomized investigation
- Efficacy of intra-articular injection of Autologous MAT

- 20 patients,
- 40-80 years old with late-stage knee OA,
  - 16 patients grade IV,
  - 4 patients grade III

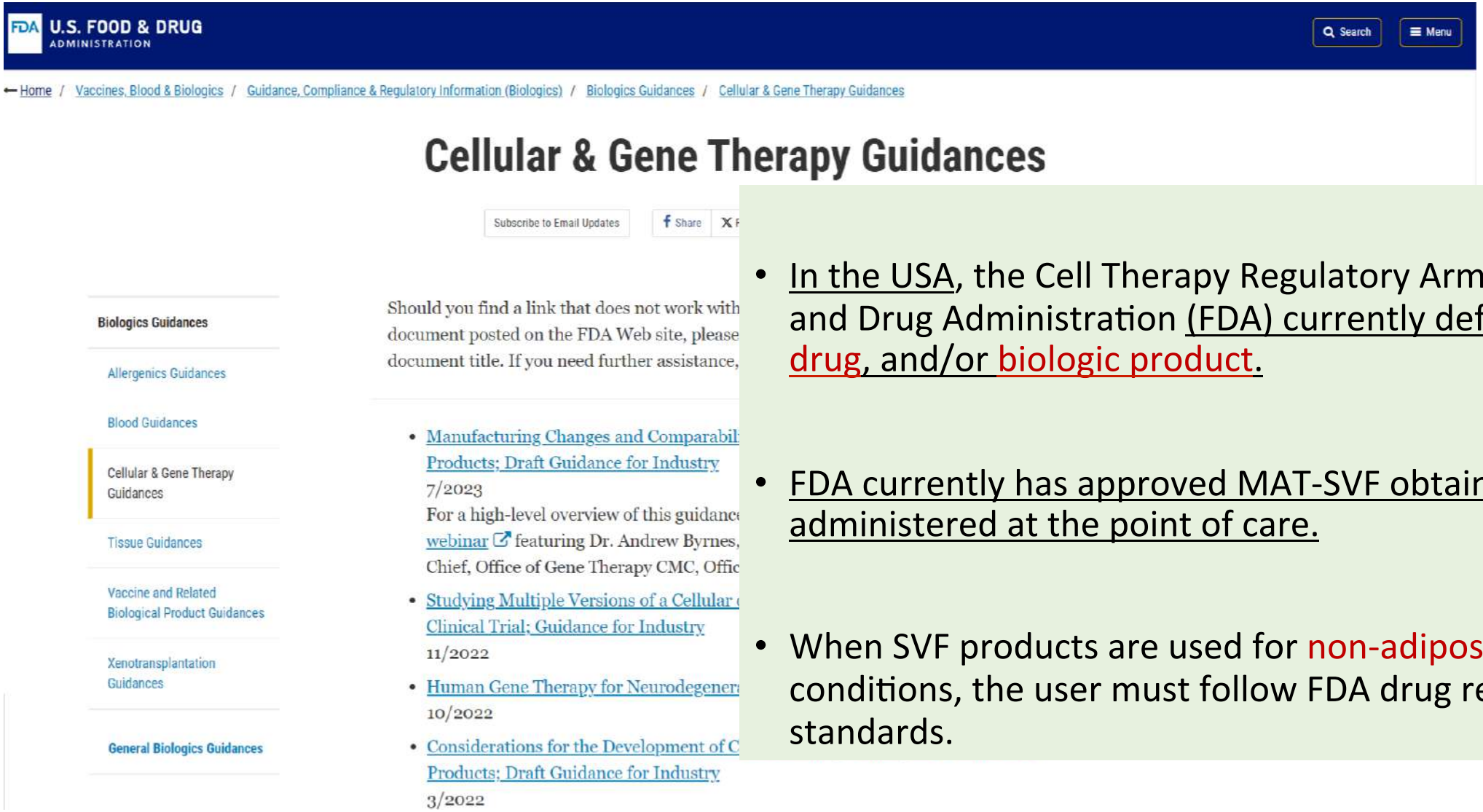
- Follow-up time ---> 12-months.

TABLE 1. The initial comparison of all Knee Injury and Osteoarthritis Outcome Score (KOOS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) related variables between baseline and 12-months follow up (mean ± standard deviation)

Clinical score	Baseline	12-months follow up	*P* (paired)	Average percent change
KOOS Pain_1	38.69 ± 17.34	64.57 ± 15.38	<0.001	+66.9
KOOS Symptom_1	47.76 ± 17.88	69.84 ± 15.91	<0.001	+46.2
KOOS ADL_1	39.6 ± 19.5	64.25 ± 17.84	<0.001	+62.2
KOOS Sport/Rec_1	16.25 ± 15.55	34.69 ± 20.85	0.003	+113.5
KOOS QOL_1	13.28 ± 12.68	36.7 ± 19.24	<0.001	+176.4
WOMAC PAIN_1	11.88 ± 3.76	6.5 ± 3.35	<0.001	-45.3
WOMAC STIFFNESS_1	4.31 ± 1.89	2.56 ± 1.46	0.001	-40.6
WOMAC PHYSICAL FUNCTION_1	39.19 ± 14.2	23.19 ± 10.85	<0.001	-40.8
WOMAC TOTAL SCORE_1	55.38 ± 18.83	32.25 ± 14.62	<0.001	-41.8
VAS resting_1	4.06 ± 2.35	0.75 ± 1.65	<0.001	-81.5
VAS movement_1	7.38 ± 1.41	3.38 ± 1.89	<0.001	-54.2

- 3 patients (15%) received a total knee replacement.
- 17 patients (85%) showed a significant improvement in their WOMAC and KOOS scores.
- Depicts a positive effect of MAT on late-stage knee OA.

Regulatory Challenges



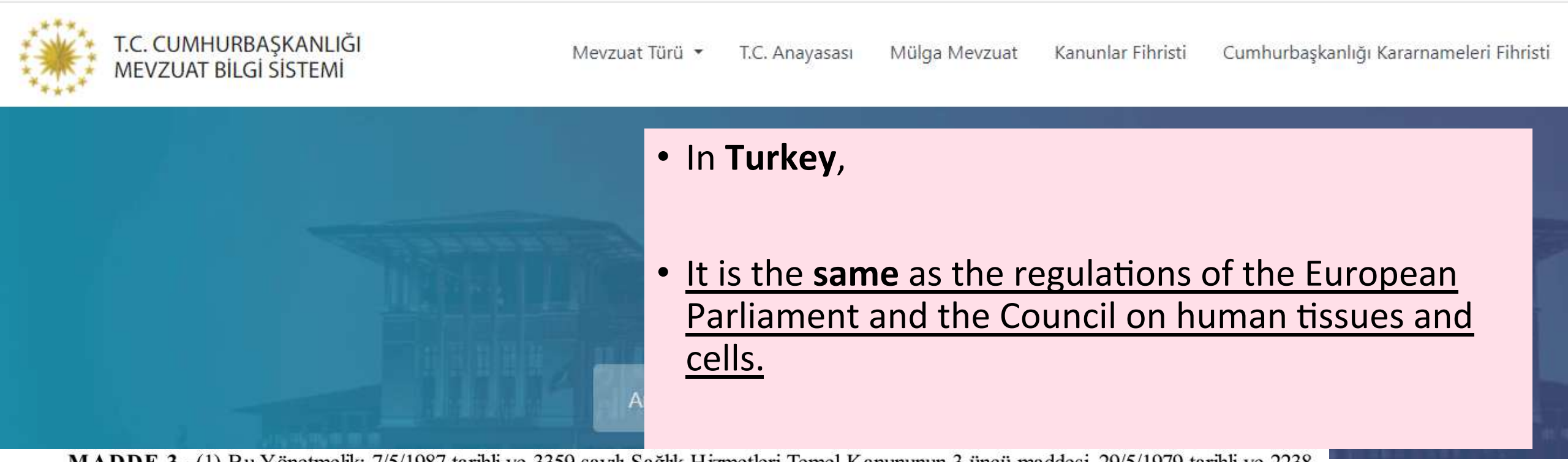
- In the USA, the Cell Therapy Regulatory Arm of the Food and Drug Administration (FDA) currently defines SVF; as a drug, and/or biologic product.
- FDA currently has approved MAT-SVF obtained and administered at the point of care.
- When SVF products are used for non-adipose-related conditions, the user must follow FDA drug regulatory standards.

Regulatory Challenges

- In Europe, SVF and other cellular products are classified as advanced therapy medicinal products (ATMPs) and strictly regulated through the European Medicines Agency (EMA).

- However, the Directive 2004/23/EC and 1394/2007 of the EMA lowered the bar on autologous SVF treatment conducted in the same surgical procedure, as such that essential functions of cells as in the donor's adipose tissue are preserved.

Regulatory Challenges



- In **Turkey**,
- It is the **same** as the regulations of the European Parliament and the Council on human tissues and cells.

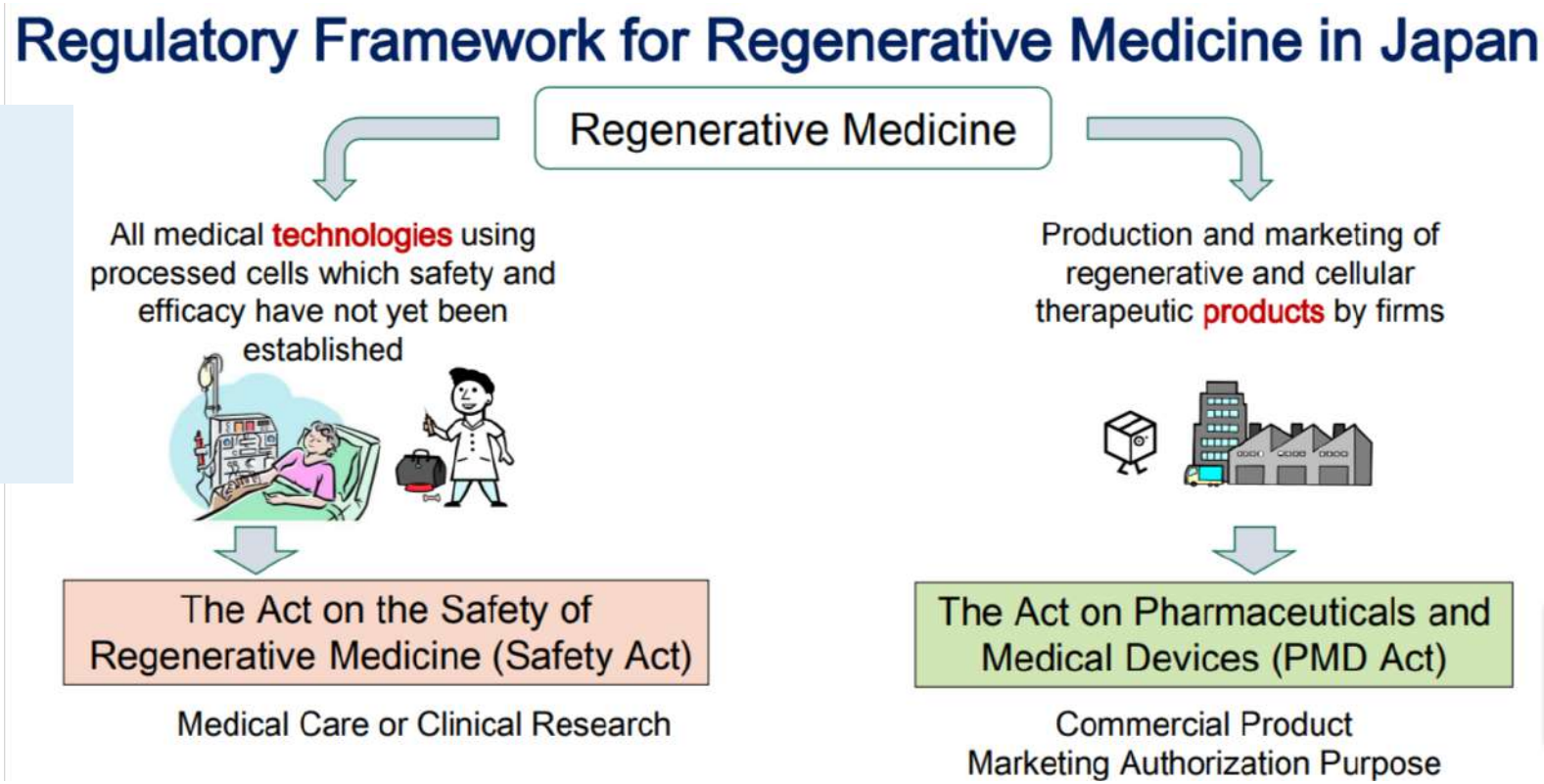
MADDE 3 –(1) Bu Yönetmelik; 7/5/1987 tarihli ve 3359 sayılı Sağlık Hizmetleri Temel Kanununun 3 üncü maddesi, 29/5/1979 tarihli ve 2238 sayılı Organ ve Doku Alınması, Saklanması ve Nakli Hakkında Kanun ile 13/12/1983 tarihli ve 181 sayılı Sağlık Bakanlığının Teşkilat ve Görevleri Hakkında [redacted] tır.

(2) [redacted] amacıyla Avrupa Parlamentosu ve Konseyi'nin insan doku ve hücreleri [redacted] mleri göz önünde bulundurularak hazırlanmıştır.

2004/23/EC, 2006/17/EC ve 2006/86/EC

Regulatory Challenges

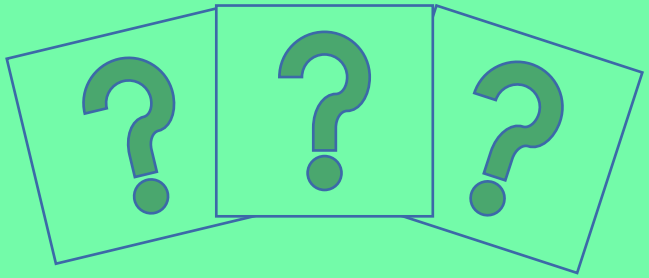
- In most **Asian countries,** SVF is considered a low-risk therapy.



Limitations

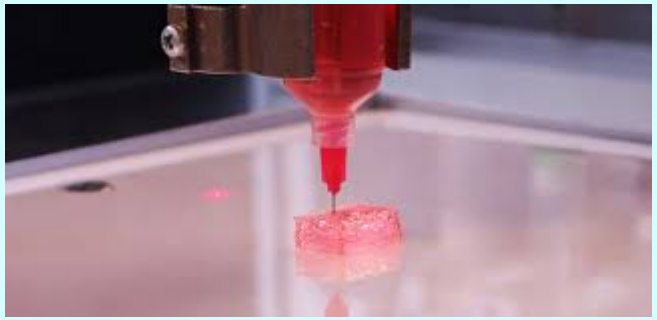
- No gold standard protocol for SVF
- No standard dose, strength, and purity
  - Variabilities in cell counts, proportions.
  - Variabilities in therapeutic dosages and outcomes.
- Majority ----> preclinical investigations and case reports
  - Mostly autologous
  - Allogeneic SVF may pose serious immune challenges.

Future Directions



- How long the cells stay in the joint to exert their effects ?
- Different adipose depots of the body ---> **SAME?**
- Mechanically versus enzymatically processed SVF
  - Regenerative effect
  - Importance of the cell compositions
  - Secretome composition

Future Directions



- **Advancements towards 3-D cell printing**
  - SVF-like extracellular matrix in a hydrogel scaffold
  - Injectable SVF hydrogel

THANK YOU…