ISRCTN88966184 https://doi.org/10.1186/ISRCTN88966184

Personalized treatment of knee osteoarthritis with fat tissue containing stem cells

Submission date
22/07/2022

Recruitment status
No longer recruiting

Registration date
01/08/2022

Overall study status
Completed

Last Edited
18/08/2023

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Knee osteoarthritis is the most common musculoskeletal disease affecting an estimated 640 million persons in the world aged 40 years and older. The increasing prevalence of this disease and the associated costs with prosthetics make searching for alternative treatment methods imperative.
Previous studies conducted at St. Catherine Specialty Hospital have shown great potential for the treatment of knee osteoarthritis with fat tissue containing stem cells using micro-fragmented adipose tissue (MFAT). The aim of this study is to evaluate the clinical, radiological and biological effects of fat tissue containing stem cells in the treatment of knee osteoarthritis.

Who can participate?
People aged 30-75 years old who are experiencing periodic or lasting knee pain in the last six months

What does the study involve?
Participants will undergo a detailed workup consisting of patient history, clinical examination, filling out questionnaires, radiological imaging and blood analysis. After matching the inclusion criteria participants will undergo a lipoaspiration procedure in which the surgeon extracts fat tissue from the patient's abdominal region, after which the patient will receive an injection of either fat tissue containing stem cells or hyaluronic acid as a dummy to the affected knee. At the same time, knee joint fluid will be aspirated for further analysis. Participants will be unaware of what is administered. For the group of patients that received hyaluronic acid, fat-derived stem cells will be frozen until the end of the study.
Follow-up appointments will be made at one month and six months where the participants will again have their blood drawn for analysis. Furthermore, knee joint fluid will be extracted at the one-month follow-up. They will have magnetic resonance imaging redone and will fill out clinical questionnaires at one-month and six-month follow-ups. Participants in the control group who received hyaluronic acid will be offered additional treatment with their frozen stem cells.

What are the possible benefits, what are the risks?
The benefits of stem cell therapy for knee osteoarthritis have been well documented and as mentioned above can greatly improve knee function. Albeit risks always remain with any medical

intervention, primarily, the risk of infection. However, stem cells have been shown to have antimicrobial effects and anti-inflammatory effects, therefore the risks are minimal.

Where is the study run from?
The majority of the study will be run from St. Catherine Specialty Hospital, with the help of the following participating institutions: University Hospital Center Sisters of Mercy Department for Traumatology, Clinical Hospital Merkur, Genos LTD and Labena LTD

When is the study starting?
February 2020 to August 2023

Who is funding the study?
1. St. Catherine Specialty Hospital
2. EU fund for ''Increasing the development of new products and services arising from R&D activities – Phase II" (IRI 2).''

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
KK.01.2.1.02.0173

Study information

Scientific Title
Comprehensive analysis of knee osteoarthritis treatment with microfragmented adipose tissue: A double-blinded randomized controlled trial

Study objectives
Previous studies have shown great potential for the treatment of knee osteoarthritis with fat tissue containing stem cells, using microfragmented adipose tissue (MFAT). There is a significant improvement in the patient-reported outcome measures (PROMs) assessing knee osteoarthritis after intraarticular application of MFAT. There is a statistically significant better clinical outcome after the application of MFAT compared to the application of hyaluronic acid (HA). There are substantial differences in the concentrations of certain cytokines, chemokines, N-glycans and miRNA’s in the synovial fluid and plasma of patients with knee osteoarthritis before and after autologous MFAT intraarticular application.

There is a statistically significant increase in the delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) index at 6 months after intraarticular application of

MFAT. There is no statistically significant increase in dGEMRIC index after intraarticular application of hyaluronic acid (HA).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 25/03/2022, St. Catherine Specialty Hospital Ethics Committee (Branimirova 71E, 10000 Zagreb, Croatia; +385 98 177 1967; research@stcatherine.com), ref: 22/5-I.

Study design
Multicenter interventional double-blinded randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Knee osteoarthritis

Interventions
Participants will be selected based on inclusion criteria. After which they will be randomly allocated into one of two treatment groups. One group will consist of a minimum of forty (N=40) participants who will receive microfragmented adipose tissue (MFAT). The second group will consist of a minimum of twenty (N=20) participants who will receive hyaluronic acid (HA).
Both groups will undergo the lipoaspiration procedure to ensure proper blinding. The collected adipose tissue of the participants who will receive HA will be cryopreserved until the end of the study when they will be offered to receive their MFAT, after viability analysis.
The lipoaspiration procedure will be performed under sterile conditions in the operating room. The participant will be placed lying supine on the operating table. Local anesthesia (2% lidocaine) will be applied to the area from which adipose tissue is taken and a small incision (6-8 mm) will be made. Approximately 500 ml of saline containing 50 ml of 2% lidocaine and 1 ampoule of adrenaline will be injected to reduce bleeding. A thin cannula will then be inserted through the incision and the adipose tissue will be pulled into the syringe in a controlled back and forth motion. After waiting several minutes, using a 17-G cannula connected to a negative pressure syringe, 60 ml of subcutaneous adipose tissue will be collected. After taking the adipose tissue, an elastic band will be put on the participants to avoid the formation of subcutaneous hematomas. The lipoaspirate will then be put into the Lipogems System (Lipogems, Milan, Italy) from which the MFAT will be obtained.

The same injection procedure will be used for both treatments. With the participant lying down, the affected knee will be extended and the femur condyle marked with a surgical marker. After disinfection of the puncture site, a caliber 21 needle will be inserted into the synovial space of the knee joint under ultrasound guidance and MFAT or HA will be administered through the needle.

The treatment group (N=40) will receive a 7 mL of autologous MFAT. The control group (N=20) will receive hyaluronic acid (Hyalubrix 60®). Owing to the nature of the procedure and to ensure proper objectivity of treatment efficacy, the participants will not know if they received HA or MFAT.

Intervention Type
Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
Autologous microfragmented adipose tissue

Primary outcome(s)
Knee symptoms, pain and function measured by patient-reported outcomes measures (PROMs) using a visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC), Oxford Knee Score and Tegner/Lysholm knee score at baseline, 1-month and 6-month follow up

Key secondary outcome(s))
1. Articular cartilage glycosaminoglycan content is measured indirectly using Delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) at baseline and 6-month follow-up
2. Osteoarthritic changes of the knee assessed using the Magnetic Resonance Imaging Osteoarthritis Knee Score (MOAKS) at baseline, 1-month and 6-month follow-up
3. Concentration of cytokines and chemokines in synovial fluid measured using a personalized panel for multiplex enzyme-linked immunosorbent assay (ELISA) at baseline and 1-month follow-up. The panel will include: IL-1β, IL-1Ra, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17A, IL-18, IL-21, IL-22, TNF-a, IFN-γ, TGF-β1, TGF-β2, MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-13, TIMP1, TIMP2, TIMP3, TIMP4, sICAM-1, V-CAM1, VEGF, ADAMTS-4, ADAMTS-5, COMP, CTX-I, CTX-II, Leptin, CCL2 (MCP1), CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (MCP-3), CXCL-12 (SDF-1).
4. Concentration of cytokines and chemokines in plasma measured using the personalized panel for multiplex ELISA at baseline, 1-month and 6-month follow-up
5. miRNA expression profile in synovial fluid analyzed using next-generation sequencing at baseline and 1-month follow-up
6. miRNA expression profile in plasma analyzed using next-generation sequencing at baseline, 1-month and 6-month follow up
7. N-glycans in synovial fluid measured using ultra-performance liquid chromatography (UPLC) system with fluorescence (FLR) detection at baseline and 1-month follow-up
8. N-glycans in plasma measured using ultra-performance liquid chromatography (UPLC) system with fluorescence (FLR) detection at baseline, 1-month and 6-month follow up
9. Phenylalanine concentration measured using tandem mass spectrometry in the plasma at baseline, 1-month and 6-month
10. Concentration of cytokines and chemokines in microfragmented adipose tissue (MFAT) is measured using the personalized panel for multiplex ELISA at baseline
11. miRNA expression profile in MFAT analyzed using next-generation sequencing at baseline
12. N-glycans are measured in MFAT using UPLC-FLR at baseline

13. Cellular ratios between pericytes, endothelial progenitors, mature endothelial cells and supra-adventitial-adipose stromal cells in the samples of MFAT measured using flow cytometry at baseline
14. Cell viability (in general) analyzed for the samples of MFAT using manual cell counting with trypan blue 6 months after cryopreservation

Completion date
31/08/2023

Eligibility

Key inclusion criteria
1. Patients with osteoarthritis of the knee who are aged 30-75 years old
2. Osteoarthritis grade 2-3 based on Kellgren-Lawrence classification
3. Patellofemoral osteoarthritis Iwano grade 2-3
4. Presence of knee pain for at least six months
5. Patients who have lower limb axis deviation less than 5°
6. The possibility of following research instructions and responding to control examinations
7. Signed informed consent for participation in the research

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
30 years

Upper age limit
75 years

Sex
All

Key exclusion criteria
1. Malignant diseases, systemic inflammatory diseases (e.g. rheumatoid arthritis, psoriatic arthritis) or other systemic diseases that can result in knee pain or cause systemic inflammation
2. A body mass index (BMI) greater than 30 or diabetes
3. Six or more painful points on the body, distributed above and below the waist, on both sides of the body and in the axilla
4. Depression (determined according to the CESD-R questionnaire)
5. Stage 4 of the Kellgren-Lawrence classification for knee osteoarthritis, stage 4 of the Iwano classification of patellofemoral arthrosis
6. A MOAKS score for synovitis or effusion less than 2 (patients without knee effusion)
7. Post-traumatic osteoarthritis
8. A history of surgery on the affected knee

9. A deviation of the mechanical axis (valgus/varus) of the lower extremities greater than 5°
10. An unstable knee
11. Damage to the meniscus or other knee structures as the main cause of pain and other symptoms (radial rupture and bucket-handle rupture of the meniscus, ACL rupture, subchondral cysts according to MRI)
12. An injury of the affected knee in the last 3 months
13. Received an intra-articular injection in the affected knee (corticosteroids, hyaluronic acid, platelet-rich plasma, etc.) within the last 3 months
14. Other musculoskeletal problems/diseases (genetic diseases such as Marfan syndrome or osteogenesis imperfecta) that would prevent clinical evaluation of the effects of MFAT or HA treatment
15. Unable to abstain from oral non-steroidal anti-inflammatory drugs (NSAIDs) for 7 days prior to MFAT or HA application and during the 6-month follow-up
16. Allergy to lidocaine and adrenaline
17. A blood coagulation disorder, thrombocytopenia or patients on anticoagulant therapy with a prothrombin time <0.70
18. Systemic immunosuppressive therapy
19. Chondromatosis or villonodular synovitis of the knee joint
20. Knee joint infection
21. Pregnancy or planning to become pregnant during the study period
22. History of chemotherapy or radiotherapy of the extremities or in the area of fat tissue extraction
23. Mental illnesses (who cannot be expected to cooperate during the project)
24. Unable to respond to follow-up examinations

Date of first enrolment
01/08/2022

Date of final enrolment
30/06/2023

Locations

Countries of recruitment
Croatia

Slovenia

Study participating centre
St. Catherine Specialty Hospital
Branimirova 71 E
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Study participating centre

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Sponsor information

Organisation
St Catherine Specialty Hospital

Funder(s)

Funder type
Hospital/treatment centre

Funder Name

St Catherine Specialty Hospital

Funder Name
EU fund for ‘‘Increasing the development of new products and services arising from R&D activities – Phase II” (IRI 2)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon reasonable request from draganprimorac2@gmail.com

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes