1) Is a policy of conventional surgical intervention more (cost) effective than prolonged conservative care in patients with at least 3 months intermittent neurogenic claudication? Does a delayed conservative policy increase costs and societal costs compared to early surgical intervention?

2) Is it possible to define subgroups of patients who will benefit substantially from one of the two proposed treatment strategies?

Methods: Population: Patients (n=280) presenting to the neurologist or neurosurgeon in the participating hospitals with at least 3 months complaints of intermittent neurogenic claudication and considering surgical treatment are eligible for inclusion.

Inclusion criteria:
- age ≥50 years old
- ≥3 months intermittent neurogenic claudication, as noted by leg/buttock/groin pain with or without back pain or fatigue in the legs provoked by walking, Leg/buttock/groin pain or fatigue needs to be strongly relieved when flexed such as when sitting in a chair
- has a narrowed lumbar spinal canal, nerve root canal or intervertebral foramen at one or more levels confirmed by MRI.

Exclusion criteria:
- has a cauda equina syndrome defined as neural compression causing neurogenic bowel (rectal incontinence) or bladder dysfunction (bladder retention or incontinence)
- has previously had a laminectomy at the same level, has degenerative or lytic spondylolisthesis ≥ grade 2 (on a scale 1 to 4) at the affected level or has significant instability of the lumbar spine

Randomization: Allocation by means of a computer-generated randomisation list.

Measurements: Follow-up measurements will be completed during the initial visit, during randomization and at 4, 26, 38, 52, 104, 156, 208, 260 weeks after randomization.

Treatments:
1) Conventional surgical intervention. Participants allocated to direct surgery will be operated as soon as possible and at the latest 4 weeks after randomization. Surgical treatment will be performed in the conventional manner with loupe magnification or microscope.
2) Prolonged conservative care. Conservative management will be a prolonged conservative treatment policy conducted by the general practitioner. The general practitioner prescribes physical therapy which will consist of active exercises to guide the patient in upgrading his or her activities according to the agreed time schedule.

Primary outcomes:
- Zurich Claudication Questionnaire
- Shuttle walking test

Secondary outcomes:
- Neurological/clinical investigations
- Modified Roland Disability Questionnaire
- Visual analogue scale for Pain in back and leg
- Perceived Recovery
- Societal costs and utilities (EuroQol-5D, visual analogue scale)
- Complications
- Re-operation incidence
- Operative data
- Imaging findings

Analyses: Data analysis will be performed based on the intention to treat principle. The answer to the main research question will be assessed with a repeated-measures analysis of variance. For the cost-effectiveness analysis a societal perspective will be taken, including health care costs, patient costs and societal costs due to lumbar stenosis related disability (e.g. inability to work and utilities expenses).

Stem Cells, Tissue Engineering & Repair

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MICROSINCE GUIDANCE AND ITS EFFECT ON HUMAN MESENCHYMAL STEM CELL ALIGNMENT AND CHONDROGENESIS

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Purpose: Tissue engineering is a possible method for long-term repair of cartilage lesions, but current tissue engineered cartilage constructs have inferior mechanical properties compared to native cartilage. We suggest that the lack of an anisotropic, oriented microscale structure in the constructs that is present in the native tissue contributes to inferior mechanics.
**Conclusions:** The microfabrication and collagen soft-lithography techniques combined with crosslinking allowed high fidelity formation of micro-sized channels on collagen membranes down to the smallest channel designed (25 μm). The channels supported the viability of MSCs, while selective cell attachment was ensured by the Pluronic treatment. Alignment of MSCs along the length of the 25-100 μm channels and alignment of collagen type II along the contours of the cell membrane within these channels show the ability of these channels to influence cellular orientation, which can lead to the alignment of ECM. To determine if the produced ECM exhibits enhanced mechanical properties, mechanical testing comparing oriented and random ECM produced in this system will be conducted in future studies.

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**INDUCTION OF MESENCHYMAL PROGENITOR CELLS WITH CHONDROGENIC PROPERTY FROM MOUSE iPS CELLS**

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**Purpose:** Although cell transplantation therapy using mesenchymal stem cells (MSCs) is considered as a prominent strategy, one of the major problems is the limited proliferative activity. Recently, induced pluripotent stem (iPS) cell line was developed as an alternative way due to their potential proliferating infinitely. However, the method to induce lineage-restricted differentiation has not been well examined.

**Methods:** iPS cells were maintained on mouse embryonic fibroblast feeder layers. To induce mesenchymal cells, we used embryoid body (EB) formation followed by culture on gelatin-coated plates. We further introduced micromass culture system to induce chondrocytes.

**Results:** The cultured adherent cells maintained multiple differentiation properties to osteoblast, adipocytes and chondrocyte. (A) Alizarin red staining showed calcium deposition in osteoblast differentiation culture at day 10 of differentiation, and (B) oil red-O staining showed lipid accumulation in adipocyte differentiation culture at day 10 of differentiation. (C) Histological and immunofluorescent characterization of chondrocyte obtained by pellet culture of the cultured adherent cells. They also possessed chondrogenic property, including Sox-9, aggrecan and type 2 collagen mRNA expressions.

**Conclusions:** These results demonstrate the property of iPS cells as an alternative candidate for treatment of cartilage degradation.

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**PROLIFERATION, DIFFERENTIATION, AND SURFACE MARKER EXPRESSION PATTERNS OF MESENCHYAL STROMAL CELLS FROM OSTEARTHRITIC VERSUS HEALTHY DONORS**

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**Purpose:** Osteoarthritis (OA) is one of the most frequent musculoskeletal disorders and represents the main indication for total joint Arthroplasty. Multipotent mesenchymal stromal cells (MSCs) can be easily isolated and culture expanded from bone marrow aspirates and provide an excellent source of progenitor cells. To assess whether advanced-stage OA affects MSCs’ suitability for musculoskeletal regenerative therapy we compared proliferation and differentiation potential as well as surface marker expression patterns of MSCs from osteoarthritic versus healthy donors.

**Methods:** MSCs were isolated from bone marrow aspirates (50 cc each) obtained from the pelvic compartment of n=14 advanced-stage idiopathic hip osteoarthritic (Kellgren and Lawrence grade 3 or 4, mean age 67±6 years) and n=15 age-matched (61±4 years) healthy donors by Ficoll gradient-separation and plastic adherence. OA was objectified radiologically (only OA group) and by use of algofunctional indices (i.e. Western Ontario McMaster Universities OA index, Harris Hip Score, EuroQol-5D). MSCs were cultured in basic (DMEM, 10% fetal calf serum), osteogenic, adipogenic, or chondrogenic medium for up to 21 days. For all assays low-passage (≤3) MSC populations were used. Proliferation was assessed by total DNA quantification, FACs analysis and CFU-F assay. Differentiation was assessed immunocytoologically, by cell-specific alkaline phosphatase (ALP) activity assay, and by osteogenic (Runx-2, ALP, BSP2), chondrogenic (Sox9, Colla, ColX), and adipogenic (PPARγ, FABP4) quantitative marker gene real-time RT-PCR analysis. For expression analysis of selected MSC-specific surface markers mean fluorescence intensities and percentages of positive cells were determined using a BD LSRII flow cytometer. Overall statistical significance was defined as p<0.05 (two-sided) based on all pairwise comparisons. The study was approved by the local institutional review board (protocol #EK203082008).

**Results:** Algofunctional scores of osteoarthritic donors were lower compared to healthy donors (p<0.0001). No significant intergroup differences were observed concerning the proliferation potential, cell-specific ALP activity and adipogenic and osteogenic differentiation marker gene expression. Interestingly SOX9 gene expression levels were increased in MSCs from OA patients after 14 day cultivation in chondrogenic medium compared to MSCs from healthy donors (p<0.01). Expression levels of CD73, CD90, and STRO-1 were elevated in respect of the negative control cellular surface antigens CD14, CD34, and CD45 in MSCs derived from both osteoarthritic and healthy donors (p<0.0001). Notable, MSCs from OA patients showed decreased levels of CD166 expression compared to cells from healthy donors (p<0.05).

**Conclusions:** The regenerative potential and surface marker patterns of MSCs from osteoarthritic donors are comparable to MSCs from healthy donors. However, the observed reduced CD166 expression levels as well as the increased Sox9 gene expression levels in OA-MSCs warrants further investigation. These data will help to facilitate the application of autologous cell-based strategies for musculoskeletal tissue regeneration.