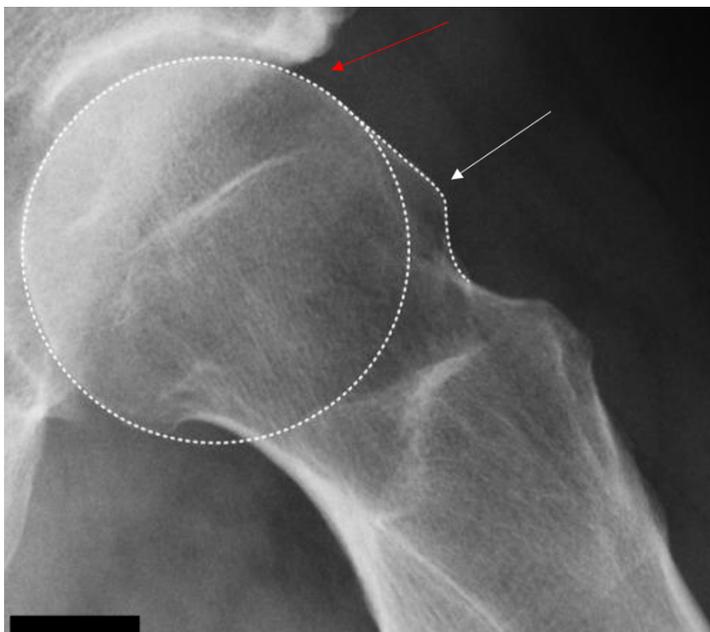


Mesenchymal stem cells to improve regeneration after joint-preserving hip surgery

The development of hip osteoarthritis is often the consequence of a congenital or acquired deformity of the lower leg or the pelvis. The most common causes are hip dysplasia or the so-called femoroacetabular impingement. Due to the deformity, there is damage of the cartilage in younger years (20-40 years) through an increased mechanical load on the cartilage of the hip joint. This excessive mechanical load leads to degenerative changes of the cartilage and to an inflammation which in turn results in changes of the whole joint including the synovial membrane, the bone and the capsule, causing osteoarthritis of the hip.

Hip dysplasia is a congenital deformity in which the head of the hip is not surrounded by the acetabulum. This leads to instability and shear forces with an increased load on the chondral layer. The combination of the reduced joint surface and the shear forces can lead to an early osteoarthritis of the hip.

The situation is comparable in hip pain that is due to an impingement syndrome. In this condition there is an excessive bone on the head of the hip (white arrow) or on the acetabulum. These deformities most often occur in teenagers and are more common in patients with high sporting activity. Due to the excessive bone on the bones, especially in high flexion of the leg there is impingement between the femur and the acetabulum. As a consequence of the repeated hits of the femur on the acetabulum, the underlying cartilage on the acetabulum is injured (Red arrow). The damage is predominately on the edge of the acetabulum and does not heal anymore and leads to an osteoarthritis of the hip.



Hip arthroscopy has been established and standardized in the past 15 years and offers the possibility to remove the excessive bone minimally invasive. This leads to reduced pain and better range of motion as it could be shown in highly qualitative scientific (1,2). In hip dysplasia, corrective osteotomies of the bones can lead to a physiological position of the bone and with this to reduced pain. These good results were mainly seen in patients without pronounced degenerative changes of the cartilage of the hip.

However, cartilage damages tend to progress even if the mechanical loads in the hip joint are normalized through correction of the deformity. This is especially the case in patients who already show a progressive degeneration of their chondral layer. Especially in patients with pronounced degenerative changes this progression may require the implantation of a hip prosthesis in young years.

The reason for this progression after correction is not yet known, a biological reason is probable. Current research hypothesizes that focal damage to cartilage leads to a progressive degenerative reaction that affects the entire joint. This degeneration seems to continue in some patients even after the mechanical load has normalized. Beside the mechanical correction, the hip joint needs a biological therapy with “rejuvenation” to stop the progression of the osteoarthritis.

Mesenchymal stem cells (MSC) have been the focus of orthopaedic research in recent years. They are located in the mesenchyme (connective tissue such as muscles, fat and bone) as silent stem cells close to the blood vessels and often wait years before they are needed. If the tissue is harmed, stem cells are required. These cells are also called mesenchymal stroma cells. In patients with osteoarthritis, there are not enough cells that are attracted to the joint. Numerous high qualitative studies have shown a reduction in the progression of osteoarthritis and pain through the use of MSCs in the knee. (3-9). Some studies show the same effect in the hip joint (10-11) They can differentiate into host tissue (cartilage), however new research shows that the cells act as sensors and take over the role of regulators. They activate the help, reanimate the local cells and coordinate a cellular and enzymatic cleaning of the tissue as well as try to limit the tissue damage. Furthermore, MSCs attract new cells that build blood vessels, they promote the development of regenerative tissue and cooperate in a limited manner in this part (12).

This effect seems to be missing after the surgeries described above and is probably the reason for the progression of osteoarthritis (9-11).

At ECOM we treat patients with MSCs derived from the fatty tissue. In a very short anaesthesia 50-100 ml of fat is suctioned from the belly. Through a complex but standardised process, the fat is treated mechanically and with a special enzyme. In this way, over 10 million MSCs can be extracted after 1 hour and applied to the joint (13,14). The cells can also be injected after joint surgery. Four to six weeks after the operation, the cells are harvested and applied. This optimises the biological milieu in the joint and thus improves the regeneration of the joint and resistance to the development or progress of osteoarthritis. The intervention can be performed as an outpatient procedure. After the treatment, no restriction regarding the weight load of the leg is necessary. In the first four weeks after the injection, sports activities are not recommended.

LITERATURE

1. Griffin DR, Dickenson EJ, Wall PDH, Achana F, Donovan JL, Griffin J, Hobson R, Hutchinson CE, Jepson M, Parsons NR, Petrou S, Realpe A, Smith J, Foster NE; FASHIoN Study Group. Hip arthroscopy versus best conservative care for the treatment of femoroacetabular impingement syndrome (UK FASHIoN): a multicentre randomised controlled trial. *Lancet*. 2018;391:2225-2235.
2. Palmer AJR, Ayyar Gupta V, Fernquest S, Rombach I, Dutton SJ, Mansour R, Wood S, Khanduja V, Pollard TCB, McCaskie AW, Barker KL, Andrade TJMD, Carr AJ, Beard DJ, Glyn-Jones S; FAIT Study Group. Arthroscopic hip surgery compared with physiotherapy and activity modification for the treatment of symptomatic femoroacetabular impingement: multicentre randomised controlled trial. *BMJ*. 2019;364:l185.
3. Freitag J, Bates D, Wickham J et al (2019) Adipose derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. *RegenMed* 14:213-230.[https:// doi.org/10.2217/rme-2018-0161](https://doi.org/10.2217/rme-2018-0161).
4. Lu L, Dai C, Zhang Z et al (2019) Treatment of knee osteoarthritis with intra-articular injection of autologous adipose-derived mesenchymal progenitor cells: a prospective, randomized, double-blind, active-controlled, phase II clinical trial. *Stem Cell Res Ther*. <https://doi.org/10.1186/s13287-019-1248-3>
5. Lee WS, Kim HJ, Kim KI, Kim GB, Jin W (2019) Intra Articular Injection of Autologous Adipose Tissue Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial. *Stem Cells Transl Med*8(6):504-511.
6. Zhao X, Ruan J, Tang H et al (2019) Multicompositional MRI evaluation of repair cartilage in knee osteoarthritis with treatment of allogeneic human adipose-derived mesenchymal progenitor cells. *Stem Cell Res Ther*. <https://doi.org/10.1186/s13287-019-1406-7>
7. Pers Y-M, Rackwitz L, Ferreira R et al (2016) Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee: a phase I dose escalation trial. *Stem Cells Transl Med*5:847-856. <https://doi.org/10.5966/sctm.2015-0245>
8. Kuah D, Sivell S, Longworth T et al (2018) Kuah D, Sivell S, Longworth T et al (2018) Safety, tolerability and efficacy of intra-articular progenitor cells in knee osteoarthritis: a randomized double-blind placebo-controlled single ascending dose study. *J Transl Med*. <https://doi.org/10.1186/s12967-018-1420-z>
9. Zheping Hong, Jihang Chen, Shuijun Zhang. Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a double-blind randomized self-controlled trial *International Orthopaedics* (2019) 43:1123-1134
10. C Dall'Oca, S Breda, N Elena, R Valentini, EM Samaila, B Magnan. Mesenchymal Stem Cells Injection in Hip Osteoarthritis: Preliminary Results. *Acta Biomed*. 2019 Jan 10;90(1-S):75-80. doi: 10.23750/abm.v90i1-S.8084.
11. Mardones R, Jofré CM, Tobar L, Minguell JJ. Mesenchymal stem cell therapy in the treatment of hip osteoarthritis. *J Hip Preserv Surg*. 2017 Mar 19;4(2):159-163. doi:10.1093/jhps/hnx011.

12. Solvig Diederichs Wiltrud Richter. Stammzelltherapie Was unterscheidet expandierte Zellen, Fettgewebsaufbereitungen und Knochenmarkaspirate? Arthroskopie 2020 Bd. 33 S 67-70
13. GE Winnier, C Alt, EU Alt et al. Isolation of adipose tissue derived regenerative cells from human subcutaneous tissue with or without the use of an enzymatic reagent. PLOS ONE | <https://doi.org/10.1371/journal.pone.0221457> September 3, 2019
14. Eckhard U. Alt, Glenn Winnier, Alexander Haenel, Ralf Rothoerl, Oender Solakoglu, Christopher Alt, Christoph Schmitz, (A comprehensive understanding of UA-ADRCs (uncultured, autologous, fresh, unmodified, adipose derived regenerative cells, isolated at point of care) in regenerative medicine. Cells 2020 Apr 29;9(5).