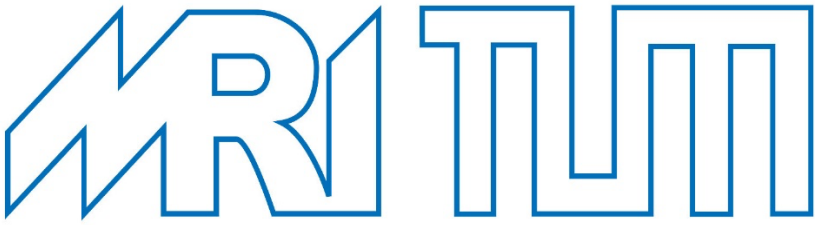

Klinikum rechts der Isar
Technische Universität München

**Clinical and Radiological Results of Management of Multilocular Cartilage lesions in the Knee Joint by Matrix Autologous Chondrocyte Transplantation (MACT)**

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Vollständiger Abdruck von der Fakultät für Medizin der Technischen Universität München zur Erlangung des akademischen Grades eines Doktors der Medizin genehmigten Dissertation

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Ethical approval for this study was obtained from the ethical committee, Faculty of medicine, Technical University in Munich, with approval number 174/15.

## English Abstract

**Background and aims:** Matrix autologous chondrocyte transplantation (MACT) is a surgical method for the treatment of full thickness cartilage defects. The efficacy of this technique on both clinical and radiological levels was shown in the literature. Our aim in this study was to show the mid-term clinical and radiological results after using this technique in multilocular cartilage lesions in the knee joint.

**Patients and Methods:** 15 patients who suffered from large multilocular full thickness cartilage lesions in the knee joint were evaluated clinically by IKDC, Lysholm, KOOS scores and Tegner activity scale. Radiologically the patients were assessed by MOCART score. Visual analogue scale was used to assess the intensity of the pain. The patients were examined and evaluated pre- and postoperatively and the different scores were documented.

**Results:** An improvement was shown in all the clinical and the radiological scores. IKDC is improved from 47.88 to 79.80%, Lysholm from 66.42 to 79.28, KOOS from 37.38 to 70.78, Tegner activity scale from level 2 to level 5, VAS was reduced from 6.86 to 1.28 and the mean MOCART score for all patients was 73.125 postoperatively. It was shown that the gender, BMI and leg axis have significant influence on the postoperative results of the patients.

**Conclusion:** MACT is an effective treatment method that is used for the treatment of large multilocular full thickness cartilage lesions in the knee joint with safety and good results both clinical and radiological levels.

# German Abstract

**Einleitung:** Die Matrixgestützte autologe Chondrozyten-Transplantation (MACT) ist eine chirurgische Technik zur Herstellung von hyalin ähnlichem Knorpelgewebe bei Knorpeldefekten. Die klinische und radiologische Wirksamkeit dieser Technik wurde in der Literatur gezeigt. Das Ziel in dieser Studie ist es, die mittelfristigen klinischen und radiologischen Ergebnisse nach Anwendung dieser Technik bei multilocularären Knorpelläsionen am Kniegelenk zu untersuchen.

**Patienten und Methoden:** 15 Patienten, die an multiplen großen Knorpelläsionen am Kniegelenk litten, wurden klinisch durch IKDC-, Lysholm-, KOOS-Score und Tegner-Aktivitätsskala bewertet. Die visuelle Analogskala wurde verwendet, um die Intensität des Schmerzes zu bestimmen. Radiologisch wurden die Patienten nach MOCART-Score beurteilt. Die Patienten wurden prä- und postoperativ untersucht und die entsprechenden Scores wurden dokumentiert.

**Ergebnisse:** Alle klinischen und radiologischen Werte haben sich postoperativ verbessert. Der IKDC verbessert sich von 47.88 auf 79.80%, der Lysholm Score von 66.42 auf 79.28, der KOOS von 37.38 auf 70.78, die Tegner-Aktivitätsskala von Level 2 auf 5, der VAS von 6.86 auf 1.28 und der mittlere MOCART-Score für alle Patienten betrug 73.125. Es konnte gezeigt werden, dass Geschlecht, BMI und Beinachse einen signifikanten Einfluss auf die postoperativen Ergebnisse der Patienten haben.

**Zusammenfassung:** MACT ist eine effektive Behandlungsmethode und wird für die Behandlung von großen multilocularären Knorpelläsionen am Kniegelenk mit Sicherheit und guten klinischen und radiologischen Ergebnissen verwendet.

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| | |
|---|---|
| ACI | Autologous Chondrocytes Implantation |
| ADL | Activity of daily living |
| AP | Anteroposterior |
| CPM | Continuous Passive Motion |
| BMP-2 | Bone morphogenic protein-2 |
| DVT | Deep vein thrombosis |
| HTO | High Tibial osteotomy |
| ICRS | International Cartilage Repair Society |
| IKDC | International Knee Documentation Committee |
| i.v. | Intravenous |
| KOOS | Knee injury and Osteoarthritis Outcome Score |
| Lat. | lateral |
| LFC | lateral femoral condyle |
| LISS | Less Invasive Stabilization System |
| MACT | Matrix Autologous Chondrocyte Transplantation |
| MFC | Medial femoral condyle |
| MOCART | Magnetic Resonance Observation of Cartilage Repair Tissue |
| MPFL | Medial patellofemoral ligament |
| MSM | Methylsulfonylmethane |
| NSAID's | Non-steroidal anti-inflammatory drugs |
| OATS | Osteochondral Autograft Transfer System |
| ORIF | Open reduction and internal fixation |
| QOL | Quality of Life |
| PDS | Polydioxanone sutures |
| Sport/Rec | Sport and Recreation |
| VAS | Visual Analogue Scale |
| Vs. | Versus |

# 1 Introduction

## Cartilage defects

Cartilage defects in hyaline cartilage is a very common and represent a demanding problem for the patients and for their treating doctors. They occur commonly after blunt trauma and ligamentous injuries. Those injuries result in impaction of the cartilage tissue causing softening, cracking and delamination of the hyaline cartilage. **(Beyzadeoglu et al., 2012)**

The incidence of cartilage lesions in the knee joint resulted either from a traumatic origin or due to cartilage degeneration and necrosis constitute about 63% of all knee pathology. About 20% of cartilage lesions are focal in nature. However, those defects affect not only the old people, but also 5% of the patients suffering from cartilage lesions are under 40 years of age and may develop grade 4 focal cartilage damage. **(Curl et al., 1997)**

About 12% of the human population suffers from cartilage lesions, these lesions can result in marked impairment of the quality of life as well as reduction in the functions of the affected Joint. **(Curl et al., 1997)**

As Joint trauma is considered as the primary cause of articular cartilage lesions; mechanism of the trauma can be either direct injury to the knee, shearing force through flexed joint or repetitive minor traumas. **(Macmull et al., 2011)**

According to Macmull et al. **(Macmull et al., 2011),** in his study, he stated that the most common knee injuries in immature knees were cartilaginous in nature. The symptoms of cartilage lesions arise from the increased load on the exposed subchondral bone after cartilage lesion not from the cartilage lesion itself, as the cartilage is aneural in nature.

There are therefore a number of different methods to treat such focal cartilage defects. In young patients, various biological methods are successfully used to treat focal cartilage defects. These methods include microfracture **(Steadman et al., 2001),** osteochondral Autologous transfer (OATS) or autologous chondrocyte implantation.

The clinical impact of those cartilage defects, and therefore the need for surgical intervention, varies according to the symptoms, age and complaints of each patient. However, the patients are commonly presented with knee pain, locking, swelling or catching of the joint, resulting in a significant reduction of the joint's function and reduction in the quality of life. Patients with articular cartilage defects are also predisposed to develop osteoarthritis with its associated disabilities and socioeconomic impact. The articular cartilage lesions may also result from chronic degenerative lesion or diseases such as osteochondritis dissecans. **(Davies-Tuck et al., 2008)**

The cartilage has limited ability to repair itself or to regenerate due to its avascular nature. Many treatment modalities have been tried to restore the function of the joints and to reduce the pain.

The cartilage differs from most other tissues in the body in its response to injury, as it is avascular tissue, its response to injury lacks the second and third phases of the classic healing response that are mediated by the vascular system (inflammatory and reparative phases). **(Newman, 1998)**

Thus, the healing capacity of the cartilage after injury is poor. Since the damage of the cartilage is thought to be a precursor to the development of osteoarthritis, this has increased the interest to find new ways to promote the repair of damaged cartilage either by repair of old lesions or by stimulation of the regeneration of new cartilage. **(Jackson & Simon, 1999)**

Matrix-induced autologous chondrocyte transplantation (MACT) is a form of tissue engineering that is used increasingly to treat damaged articular cartilage. In animal studies, it shows variable results, for examples in rabbits, the repair tissues were effectively produced **(Brittberg et al., 1996; Grande et al., 1989),** whereas, in dogs, ineffective fibrocartilage is formed over a long time. **(Breinan et al., 1997)** In human beings, the clinical symptoms were satisfactory reduced up to 9 years postoperatively **(Breinan et al., 1997),** but due to variable factors, studying the composition of the repair tissue in the MACT region is limited. **(Peterson et al., 2000; Richardson et al., 1999)**

Peterson et al. **(Peterson et al., 2000)** reported that after MACT a hyaline-like repair tissue was produced and had the most favorable outcome, while in patients who suffered from graft-failure, only fibrous tissue was detected in the defect region.

The major components of the cartilage tissue are the collagen and proteoglycan, those products give the cartilage its biomechanical properties. The collagen provides the cartilage its tensile strength and it is considered to be the main fibrous component of the cartilage, it contributes to the compressive properties of the cartilage by resisting the pressure that is created from swelling of the proteoglycans under pressure. **(Ratcliffe A., 1996)**

Finding the best way to repair the cartilage represented a big problem to the orthopedic surgeons for many years. While many methods were applied such as subchondral bone drilling or transplantation of periosteum or perichondrium in the cartilage defect area, those methods resulted in the production of soft fibrocartilage that has lower biomechanical functions as well as a poor integration with the adjacent tissues. **(Furukawa et al., 1980; Homminga et al., 1990; Ratcliffe A, 1996)**

Brittberg et al **(Brittberg et al., 1994)** reported an alternative method, which is the autologous chondrocyte implantation. Animal studies showed the production of more organized hyaline cartilage after using this method. In Sweden, the first 100 patients who were treated by this method showed very promising clinical outcome. But since the cartilage tissue has a very slow turn-over, usually a long-time follow-up is always needed. **(Brittberg et al., 1994)**

In the early stages of cartilage injury, damage of the cellular membrane of the cells will result in the efflux of the intracellular constituents, which will result in the disturbance of the cell metabolic activity and causes disturbance in the production of the proteoglycans and its concentration.

These changes will subsequently lead to hydration of the tissues and disorganization of collagen. **(Lohmander et al., 1989; Mankin H. 1994; Mankin H.1982)** and allow easier transmission of load to the area of the cartilage lesion, starting a vicious circle that will eventually change the partial thickness lesion into full-thickness lesions. **(Mow V, 1988)**

In full-thickness cartilage lesions, penetration of the subchondral bone will occur and this will allow the efflux of bone marrow cells that help in intrinsic repair. **(Goldberg & Caplan, 1999)** These bone marrow cells usually regenerate into fibrocartilage, which is biomechanically inferior to the native hyaline cartilage of the joint. **(Alford & Cole, 2005; Simon & Jackson, 2006)**

Many methods were implemented to help in the management of cartilage lesions, these methods include conservative and operative treatment. Operative choices can be divided into palliative, reparative and restorative methods, each of these methods has its specific indications and its result and depends on many factors such as surgeon's experience, patients age, duration of the complaint, associated pathology and the lesion's surface area and depth. **(Simon & Jackson, 2018)**

Generally, people with low physical demands and lesions smaller than 2 $cm^2$ are usually treated by palliative methods (arthroscopic debridement and lavage) as first line of treatment, this method leads to dilution of the pain-producing substances in the knee. While in young, active and physically demanding patients, the aim of the treatment is either reparative or restorative.

Reparative techniques include "marrow stimulation technique", this method will lead to formation of fibrocartilage. The formed fibrocartilage has lower biomechanical properties in comparison to the native hyaline cartilage of the knee and will degenerate and fail over the time resulting in the returning of the symptoms. **(Falah et al., 2010)**

In restorative techniques, the aim is to replace the damaged cartilage and or the subchondral bone with fully intact hyaline cartilage by using either chondral or osteochondral transplant or encouraging the body to form a hyaline-like tissue in the area of the lesion.

In our study, we used MACT (Matrix Autologous Chondrocytes Transplantation), a synthetic collagen membrane that is impregnated with patient's cartilage cells, we used this method in Outerbridge Grade III and IV cartilage lesions (see table 1), taking into account the size, depth of the lesion, the age and physical activity as well as the compliance of the patient. Concomitant pathologies of the knee were addressed and treated accordingly.

# Different treatment modalities of cartilage defects

## i Conservative treatment

The goal of the conservative treatment is the reduction of the symptoms and not healing of the lesions. This modality is used in the treatment of small lesions in non-operable or surgically unfit patients. **(Craig W, 2003)**

This include the use of the non-steroidal anti-inflammatory drugs (NSAID's), chondroprotective drugs as (glucosamine, chondroitin sulphate, methylsulfonylmethane or MSM, Omega-3). Calcium and vitamins, as well as intra-articular injections such as steroids and viscosupplementation are also used. There is no evidence of structural improvement with the above mentioned methods. **(Browne & Branch, 2000)**

## ii Surgical treatment

In order to withstand the high biomechanical stresses in which the articular cartilage is subjected to, it is necessary to cover the cartilage defects with tissue that is similar or nearly similar to the native hyaline articular cartilage of the joint.

The surgical treatment strategies that are currently available to treat the cartilage lesions, include palliative, reparative and restorative methods.

### Palliative method:

### Arthroscopic lavage of the knee and debridement of the cartilage lesion

This method includes smoothing of fibrillated articular or meniscal surfaces, removal of motion-limiting osteophytes and inflamed synovium as well as lavage of the joint which clears the joint from calcium phosphate crystals and other pain-producing substances. The lavage is beneficial for the group of patients presenting with acute pain, mechanical symptoms as locking and catching. **(Dearing & Nutton, 2008; Dervin et al., 2003; Evans et al., 1984; Swan A, 1994)**

Furthermore, through the arthroscopic lavage, the inflammatory mediators will be washed out and removed from the knee and this will lead to the reduction of the symptoms but only for short time. **(Jackson & Dieterichs, 2003)**

Débridement of the articular cartilage allows the removal of free and unstable cartilage fragments, as well as osteophytes to smoothen the cartilage surface. Studies showed that this method has no long-term effect and will not stop the degenerative process. **(Kim et al., 1991; Mitchell & Shepard, 1987)**

## Reparative and restorative techniques:

The reparative methods are done by stimulating the induction of the intrinsic regenerative capacity of the cartilage by marrow stimulating techniques (Pridie drilling, abrasion chondroplasty and microfracture), while the restorative measures are performed through transferring cartilage tissue to the area of the lesion as in OATS (Osteochondral Autograft Transfer System), Mega-OATS, Allograft OATS, or through the implantation of cartilage cells by injection of autologous cartilage cells in the area of the lesion under a periosteal patch as in ACI (Autologous Chondrocyte Implantation) or through the implantation of collagen membrane that is impregnated with autologous cartilage cells (Matrix Autologous Chondrocyte Transplantation).

## Marrow stimulation techniques Fig. 1

The articular cartilage has a limited capacity of regeneration and it is nourished by diffusion from the capillary network of the perichondrium of the subchondral bone as well as from synovial fluid.

Based on these concepts, the following procedures were developed to reduce the symptoms or to promote the reparative capacity of the hyaline cartilage. **(Mankin H., 1982)**

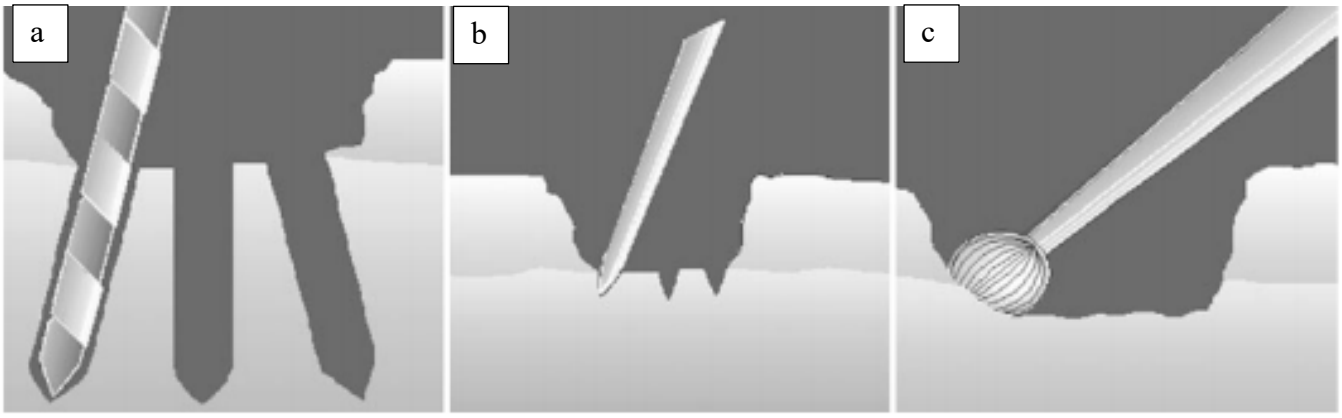



Figure 1 Marrow stimulating techniques: from a to c Pridie drilling, Microfracture, Abrasion arthroplasty **(Resinger et al., 2004)**

### Pridie drilling

Through drilling of holes in the subchondral lamellae of the defect area, the fibrocytes and stem cells will migrate and move from the underlying spongy bone to the defect area and will form a super clot that contains growth factors that will differentiate into fibrocartilage. **(Goldman et al., 1997)**

However, this regenerate is biomechanically inferior to the native hyaline cartilage and cannot withstand the stresses in which the knee might be subjected to and will eventually fail after some time. **(Hice et al., 1990; Schmidt & Hasse, 1989)**

**Microfracture**

Similar technique is used in the Microfracture with special instrument for opening of the subchondral bone lamellae. **(Steadman et al., 2003) Fig. 1-b, 2, 3**

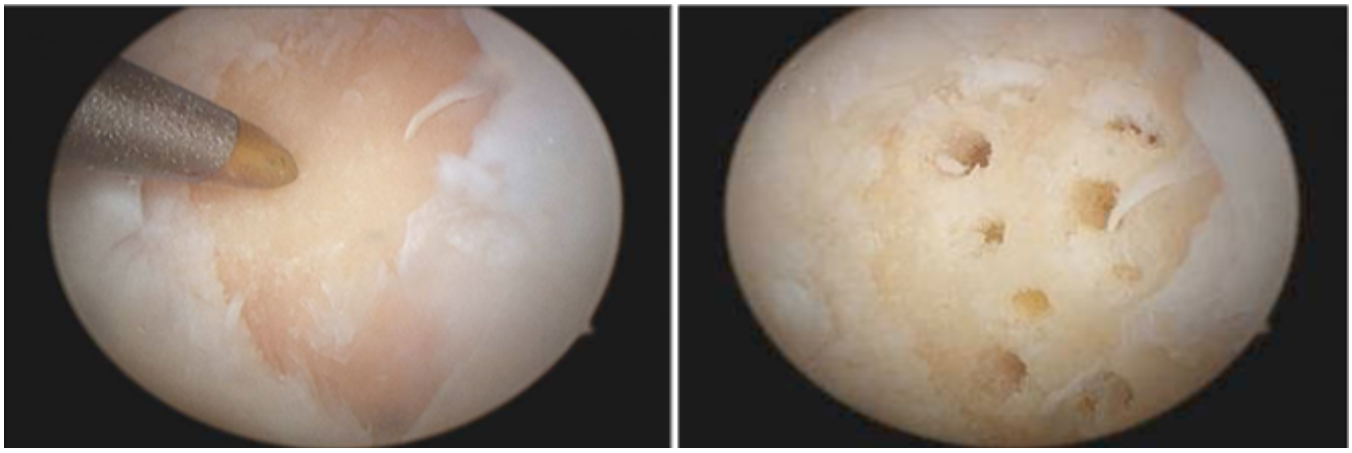


Figure 2 Microfracture technique **(Steadman et al., 2003)**

The Microfracture is the most studied reparative method. The idea of the microfracture is controlled opening of the subchondral bone plate to allow the efflux of stem cells and growth factors to the area of cartilage defects. **(Steadman et al., 2001; Steinwachs et al., 2008)**

The released cells and growth factors promote the formation of fibrin super-clot, that allow the differentiation into fibrocytes and then the development of fibrocartilage. This type of cartilage contains a high amount of collagen type I, which has inferior biomechanical features than collagen type II which is found in the native hyaline cartilage and supplies promotes its ability to resist compression and shear load. **(Bedi et al., 2010)**

The ideal indications for microfracture include contained cartilage lesions in young active patients, single lesion in 1 compartment of the knee, GII or III cartilage lesions that are less than 2cm$^2$ in its size. (**Mithoefer et al., 2005)**

The remained affected cartilage in the defect area is removed arthroscopically by removal of the calcified layer, then creating a well-defined, sharp borders of healthy cartilage to provide the best mechanical condition that will reduce the shear and compressive forces on the formed fibrocartilage. Then, a surgical awl is used to form small perpendicular holes that are spaced 2 to 3 mm apart. **(Cole et al., 2009; Steinwachs et al., 2008)**

The proper drilling depth is performed when the influx of the arthroscopic fluid is decreased as well as the efflux of blood and marrow elements from the drilled holes. **Fig. 3**

Steadman et al, **(Steadman et al., 2003)** in their published long-term study with a follow-up of 11 years in 72 patients (75 knees) who underwent a microfracture, reported improvement in 80% of the patients using multiple clinical outcome measures. Similarly, Mithoefer et al, **(Mithoefer et al., 2005)** reported that 67% of 48 patients, with a mean follow-up time of 3.6 years, reported

good to excellent functional improvements. The authors found that an age of less than 35 years, a body mass index of less than 30 kg/ $m^2$, and defect size of less than 2 $cm^2$ and defect location of the medial femoral condyle, showed more successful outcomes with microfracture. **(Cole et al., 2009; Gudas et al., 2005; Mithoefer et al., 2005; Steadman et al., 2003)**

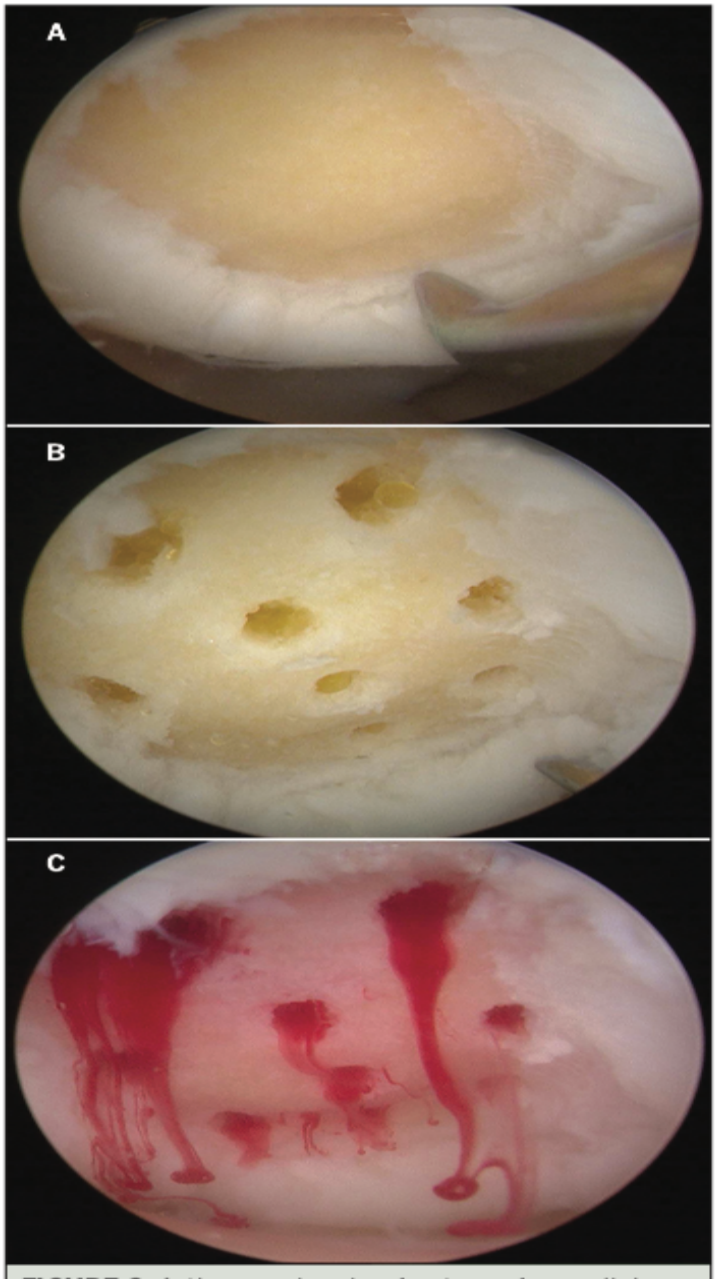



Figure 3 Arthroscopic microfracture of medial femoral condyle **(Tetteh et al., 2012)**

a- After preparation of cartilage lesion, b- after puncturing of the subchondral bone, c- efflux of the blood and marrow components

**Abrasion chondroplasty: Fig. 1-c**

In this method the degenerative cartilage is removed by arthroscopic shaver without opening the subchondral bone, this method helps in relieving symptoms only for short time and will not stop the degenerative process. **(Steadman et al., 2003)**

## Cartilage tissue transfer

### Osteochondral Autograft Transfer System (OATS)

A deeper defect that extends and involves the subchondral bone will require a different approach as osteochondral autograft or allograft transplantation.

This procedure is recommended and indicated for symptomatic, unilocular lesion that is smaller than $2cm^2$ in a non-arthritic knee with upper-age limit 50 years old, with proper limb alignment, intact meniscus. In case of meniscus lesions and limb malalignment, they should be addressed primarily to avoid premature wear of the transplanted osteochondral tissue. **(Hangody et al., 2008)**

OATS can be done arthroscopically or via mini-arthrotomy, the site of harvested cartilage is either from medial trochlea (which has the lowest contact pressure), lateral trochlea or intercondylar notch. **(Hangody et al., 2008)**

There are different sizes of harvesters for donor and recipient sites available in the surgical instruments' set to provide press-fit grafts. The harvester is positioned perpendicularly to the donor site and advanced approximately 15 mm into the subchondral bone. The donor plug is carefully and gently extracted from the donor site in order not to shear the harvested tissue.

Then the recipient site is prepared with recipient socket, which is advanced 2 mm less in depth than the donor harvester. Once the recipient site is prepared, the graft is inserted gently in a press-fit manner using appropriate force to avoid damage of the transferred tissue. **(Cole et al., 2009) Fig. 4 (a-e) (Imhoff, et al., 1999)**

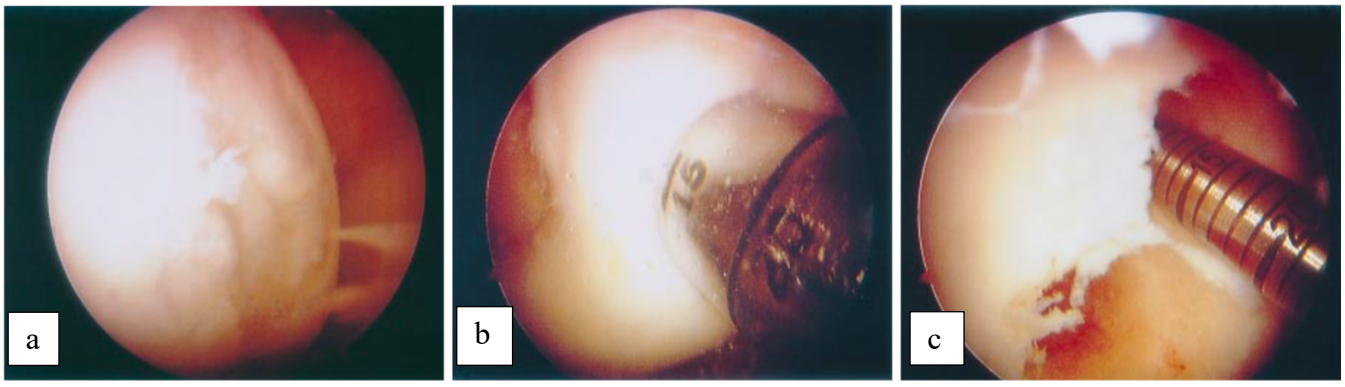
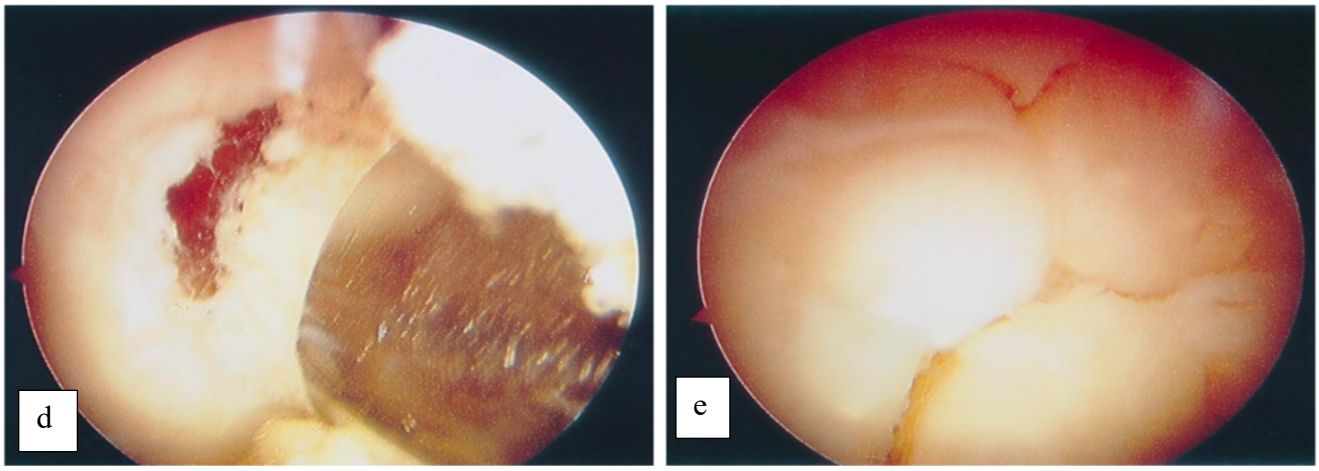



Figure 4 Osteochondral defect in the loading zone medial femoral condyle in a 25-year-old patient **(Imhoff, et al., 1999)**

a-The size and extent of the defect is evaluated arthroscopically, b- Removal of osteochondral cylinders from the harvest area with a depth of 15 mm. c- After fine adjustment of the recipient sites, the re-implantation depth is measured in relation to the surrounding healthy cartilage.




d- Carefully driving in and precisely fitting the harvested tissue cylinder in Press-fit technique into the recipient area, e- In case of multiple osteochondral transfers, the other donor cylinders are implanted directly adjacent to each in order to fill the defect completely in a press-fit manner, possibly with different cylinder sizes.

Hangody et al, **(Hangody et al., 2008)** reported good to excellent results with osteochondral autograft in 92% of patients with femoral condyle defects and in 74% of patients with patellar defects. Additional studies reported good to excellent outcomes of osteochondral autograft in 93% of Talar dome lesions.

Mega OATS operation is used to treat the larger osteochondral lesions in the weight-bearing zones of the femoral condyles by transferring osteochondral grafts from the posterior femoral condyle **(Fig. 5**). **(Imhoff, et al., 1999; Minzlaff et al., 2010)**

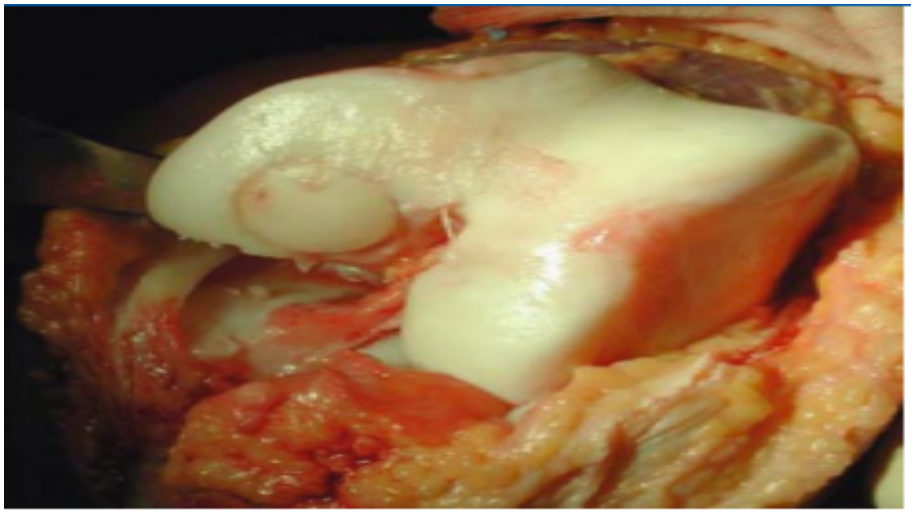


Figure 5 Transplanted Mega-OATS **(Minzlaff et al., 2010)**

### Osteochondral Allograft Transplantation

Osteochondral allograft transplantation is fresh, cold-preserved cadaveric osteochondral tissue used in lesions slightly larger than 2 $cm^2$ **(Ahmed & Hincke, 2010)**. Its Advantage includes avoidance of donor site morbidity. The disadvantages include the graft and cell viability (depends mainly on the correct preparation and preservation technique of graft tissues) and the risk of disease transmission.

The majority of the used osteochondral allografts are fresh rather than frozen. The Fresh allografts are stored in a physiologic medium at 4°C to maintain the viability of chondrocyte. Due to variable reasons, this method is strictly used with limitation in Germany.

## Transplantation of cartilage cells

### Autologous chondrocyte implantation (ACI)

Autologous chondrocyte implantation was first introduced in 1987 in Sweden by Lars Peterson and Mats Brittberg **(Brittberg et al., 1994)** as the first attempt for a cell-based biological approach to treat large and deep cartilage defects.

Attempts were done to cover the cartilage defects with perichondrium or periosteum; the idea was used to benefit from the chondrogenic potency of the perichondrium. According to Nehrer et al. this procedure has non-satisfactory results in long-term follow-up. **(Nehrer et al., 1999)**

It is a two steps procedure. In the first step, an arthroscopic knee evaluation is done; if coexistent lesions are found, they are addressed and treated accordingly, the a cartilage sample is harvested from less weight bearing area (usually medial rim of the trochlea) and then cultured in a special media in the laboratory for 2-3 weeks to form a cell suspension.

In the 2nd step, the defect is exposed through parapatellar arthrotomy, then the lesion is well prepared and diseased cartilage is removed. A periosteal patch is taken from the proximal part of the medial surface of the tibia, then it is sutured over the cartilage defect. After that, the cell suspension is injected under the periosteal patch and finally the injection site is sealed with sutures and fibrin glue. **(Peterson et al., 2010)**

The use of the periosteum showed some disadvantages as increased morbidity at the harvesting site (proximal tibia) and hypertrophy of the membrane, which produced painful clicking, this occurred in approximately in 25% of patients, who needed after that an arthroscopic resection of the hypertrophied periosteum. **(Peterson et al., 2010)**

## Matrix autologous chondrocyte transplantation (MACT)

With the further development of the ACI, MACT was developed in which the cultivated cartilage cells were implanted and distributed on a collagen matrix or membrane to avoid the drawbacks of the previous method.

Matrix Autologous Chondrocyte Transplantation (MACT) is a restorative technique that results in the formation of a hyaline-like cartilage. This technique had shown to provide relief for patients suffering from big cartilage lesions.

The MACT is a procedure that consists of 2 steps and indicated for young and middle-aged patients (15-45 years), with full-thickness cartilage lesions measuring between 2 to 14 $cm^2$ with intact subchondral bone. **(Ahmed & Hincke, 2010)**

Behrens et al. **(Behrens et al., 1999)** was the first group who succeeded to cultivate the chondrocytes on a collagen membrane. Using of collagen membrane has improved the distribution and the adhesiveness of the cartilage cells to the defect area and prevented the dedifferentiation of the cartilage cells. Contraindications to this procedure include treatment of kissing lesions, untreated pronounced malalignment, ligamentous instability and lesions that extend to involve the subchondral bone.

The first stage of the surgical procedure is done arthroscopically through which the harvesting of articular cartilage from non-weight bearing area of the knee is done as well addressing the co-morbidities as malalignment, meniscal lesions or ligamentous instability and treat them accordingly.

The harvested cartilage sample is about 200-300 mg from a non-weight-bearing region, which is transported in a nutrient medium under strict sterile measure for in-vitro chondrocyte differentiation and expansion. The second stage is done 2-3 weeks after the first stage and includes arthrotomy to expose the cartilage lesion. The lesion is debrided by special curette to remove scar tissue that is formed in the lesion and to form vertical walls or borders that allow the later on implantation of the membrane. **(McNickle et al., 2009)**

The advantage of creating stable vertical walls is to allow the easy placement of the collagen matrix (TETEC company, Reutlingen, Germany) over the lesion site.

The collagen membrane has 2 faces, one of them contains the chondrocytes and will face the lesion, the other one is designed to prevent the influx of knee fluids into the lesion or the efflux of the cartilage cells outside the lesion.

# 2 Basics

## 2.1 Anatomy of the knee joint

The knee joint is the movable connection between the thigh and the leg, it has a complex anatomy, in addition to variety of possible movements.

## 2.2 The tibiofemoral joint

The femur ends distally in the form of two condyles and epicondyles. Ventrally, the condyles are separated by the trochlea femoris, the patellar groove, and posteriorly by the intercondylar fossa.

Furthermore, the two condyles differ in size and shape. The medial condyle is wider and extends further distally than the lateral one and because of its size and position it is responsible for the slight valgus position of the normal knee joint.

The corresponding end of the tibia is also divided into a medial and a lateral plateaus, which are separated by the tibial eminence. The medial tibial plateau is larger and extends posteriorly and it is rather flat to concave in shape. It shows a relatively adapted form for the medial condyle compared to the lateral tibial plateau with the lateral femoral condyle. The lateral plateau is slightly convex, showing only less congruence with the lateral femoral condyle. In summary, there is a bony incongruity between the distal femur and the proximal tibia. **(Flandry & Hommel, 2011)** This incongruence is improved by the two menisci. They have a crescent-shaped and are firmly anchored in the knee joint by different ligaments or connections, they nevertheless show a certain mobility **(Makris et al., 2011)** The lateral meniscus appears more circular than the medial and also shows greater mobility**. (Vedi et al., 1999)**

The menisci perform a number of tasks in the knee joint. They serve in the stability of the knee joint **(Shoemaker & Markolf, 1986).** Their most important function is the transmission of pressure in the joint. By absorbing the forces and distribute them over a larger area. **(Walker & Erkman, 1975)**

The collateral and cruciate ligaments are the main stabilizers of the knee joint. The anterior cruciate ligament originates from posterior aspect of the medial surface of the lateral femoral condyle and inserts anterior to the anterior horn of the lateral meniscus at the tibial surface. It consists of anteromedial and a posterolateral bundle. It resists the anterior tibial translation and rotational loads. **(Amis & Dawkins, 1991)**

The posterior cruciate ligament runs in a crossed direction behind the anterior cruciate ligament. This ligament originates from the lateral surface of the medial femoral condyle and the roof of the intercondylar notch, it runs through the intercondylar fossa to insert to the posterior tibia just below its articular surface. **(Amis & Dawkins, 1991)** Due to their course, the cruciate ligaments are responsible for the stability of the knee joint in the axial and sagittal planes.

The collateral ligaments stabilize the knee joint in the coronal plane. The medial collateral ligament is divided into a superficial and a deep bundle and appears flat. The superficial bundle runs from one-point posterior and proximal to the medial epicondyle to about 5-7 cm below the tibial articular surface. The deep portion of the medial collateral ligament runs from the medial condyle to the medial meniscus and from there to the tibia, this connection is partly responsible for its limited mobility. **(LaPrade et al., 2007)** The lateral collateral ligament arises posteriorly and proximally from the lateral epicondyle and extends to the lateral part of the fibula head and is 6-7 cm long. **(LaPrade et al., 2003)**

## 2.3 The patellofemoral joint

The patellofemoral joint is composed of the patella, the largest sesamoid bone in the human body, and the patellar groove and the trochlea femoris. The force of the quadriceps femoris muscle is transmitted via the quadriceps tendon to the patellar ligament and finally to the tibial tuberosity. The patella increases the lever arm acting on the knee joint and thus improves the stretchability and extension. In addition, the patella acts as a protector for the femorotibial joints. **(Tecklenburg et al., 2006)**

## 2.4 Etiology of cartilage lesions

There are 2 phenotypes of cartilage lesions; focal and degenerative. The focal lesions are well-demarcated lesions primarily caused by trauma, osteochondritis dissecans or osteonecrosis. While the degenerative lesions are poorly delineated lesions and mainly follow meniscal lesions or unstable ligamentous structure. **(Craig W, 2003)**

The trauma is considered the most common cause of osteochondral lesion of the knee; it's either due to accidents, sports' injuries or patellar dislocation. The later one is responsible for 40-50% of osteochondral lesions around the femoral condyles **(Boden et al., 1997)**

The shearing force resulted from the traumatic injuries may lead to stress fractures that may pass through the cartilage and may also extend to subchondral bone.

The osteochondritis dissecans is located often in the lateral aspect of the medial femoral condyle (85%) and may be they are idiopathic in nature or may be caused by chronic repetition of microtrauma (60%). **(Bianchi et al., 1999)**

The osteonecrosis may be primary (spontaneous or avascular) or secondary to variable factors as steroid therapy, alcoholism or post-meniscectomy. **(Patel et al., 1998)**

The other phenotype of cartilage lesions is the degenerative lesion, which has different shapes and depths. The stiffness of the subchondral bone will result in less shock absorption by the bone and the shock will be mainly absorbed by the cartilage. Cartilage matrix breakdown will

eventually follow, with continuous and further weight bearing; the cartilage lesion will increase in size, till exposure and abrasion of the subchondral bone takes place. **(Craig W, 2003)**
The ligamentous instability of the knee particularly after ACL injuries or after the loss of the mechanical functions of the meniscus after meniscectomy or after meniscal lesions will lead also to degenerative cartilage lesions. **(Stanitski, 1995)**

Lewandrowski et al. **(Lewandrowski K, 1997)** reported that articular cartilage lesion is accompanied with meniscal tears in 76% of cases, more commonly after longitudinal meniscus tears than horizontal tears

## 2.5 Morphology of the cartilage

There are structural differences between the cartilage in adults and adolescents. In adults, the cartilage is demarcated into calcified and non-calcified layers. When shearing forces are transmitted to cartilage in adults, a chondral fracture will result, while in adolescents, the cartilage is not calcified, thus the forces that are transmitted through subchondral bone will result in an osteochondral fractures. **(Macmull et al., 2011)**

There are 3 different types of cartilage in human beings, which differ in the matrix composition, structure, and functions,

1- Hyaline cartilage, it is the most common cartilage type in humans, and it is found in ribs, nose, larynx, trachea and articular surfaces. It is a precursor for bone.
2- Fibrous cartilage, which is found in intervertebral discs, joint capsules, and ligaments.
3- Elastic cartilage, which is found in the external ear, epiglottis and larynx.

The hyaline cartilage is glassy in appearance and has a smooth surface to minimize the friction forces between the surfaces. Although it has widely dispersed collagen type II to strengthen it, it remains the weakest cartilage type.

The articular cartilage has a unique structure which can tolerate a great amount of intense and repetitive physical stresses. However different factors like mechanical, chemical and microbiological factors can damage it and often lead to the disabling process of arthritis as the articular cartilage has a very limited ability to regenerate itself even after minor injuries.

In 1743 Hunter stated that cartilage " once destroyed, never repaired", this concept stood for two and half centuries unchanged and has been strengthened with studies that described the very weak regeneration ability of the chondrocytes. **(Newman, 1998)**

### i. The structure and biology of the articular cartilage

The cartilage is composed of cells called the chondrocytes embedded in an extracellular matrix. This matrix is composed of macromolecules including collagen, proteoglycans, and non-collagenous proteins. 60-80% of matrix's aqueous weight is water, and this contributes to the mechanical properties and to the nutrition of chondrocytes through diffusion. The type of collagen found in the articular cartilage is collagen type II (90-95%).

They are two types of collagen; collagen type I which is found in bone, meniscus, tendons, cornea, skin and annulus fibrosis, while collagen type II is found in hyaline cartilage, notochord and nucleus pulposus. The hyaline cartilage consists of high content of proteoglycans and water, interacting with collagen type II forming a hydrated Matrix.

The proteoglycans exist in 2 forms either as monomers or polymers that are linked by proteins filaments to hyaluronic acid filaments. **Fig. 6**

The proteoglycans monomers are formed from central protein core that is connected to sulphated glycosaminoglycan that are hydrophilic, with negative charges (anionic) that tend to bind with positive charges (cations). Further they repeal from each other keeping the molecules in a distended state. They tend to occupy a greater volume in the free solution state in comparison with its volume in native cartilage. Here comes the importance of the collagen, being partially hydrated and act as compressors to the proteoglycans.

Theoretically, destruction of the collagen fibers will permit the proteoglycans to expand causing the matrix to swell as in chondromalacia patella. **(Newman, 1998)**

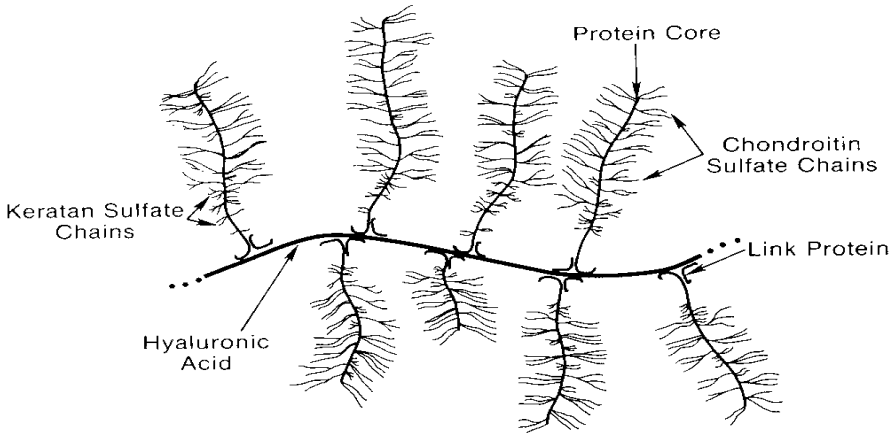



Figure 6 Proteoglycan structure **(Newman, 1998)**

## ii. Biomechanical Properties of hyaline cartilage

The hyaline cartilage is hydrated and compressed; it is composed of 2 phases, solid phase (collagen, proteoglycans, other non-collagenous proteins) and liquid phase (water and electrolytes). **(Mow et al., 1984; Newman, 1998)**

Under pressure (loading of the joint), the fluid flows out of the matrix and when the load is removed the fluid will return back to it.

The low permeability of the articular cartilage prevents any rapid squeeze or flow of the fluid out of the matrix, and that provides protection of the solid phase of the cartilage after strong and rapid impacts to the joint. **(Newman, 1998)**

## iii. The Cartilage nutrition

The cartilage nourishment takes place by diffusion, that depends on the viscoelastic properties of the cartilage. The interaction between solid and fluid phases of the cartilage promotes the transfer of the nutrients to the matrix as well as washing of the metabolites out of it.

## iv. Chondrocytes

The chondrocytes are responsible for the synthesis, maintenance, and regeneration of the matrix, while the matrix has also a direct influence on the chondrocytes. Researchers stated that in young animals the rate of proliferation and division of chondrocytes and hence the production of the cartilage matrix are more after reaching the skeletal maturity. **(Buckwalter JA, 1988)**

## v. Structural zones of the articular cartilage (Fig. 7).

It is divided into 4 zones which are superficial, transitional (middle), deep and zone of calcified cartilage. **(Aydelotte MB et al., 1988; Buckwalter JA et al., 1988; Poole et al., 1986)**.

The chondrocytes differ in size, shape and metabolic activities. **(Aydelotte MB et al 1988)** The superficial zone is the thinnest and it forms the gliding surface of the joint. It is formed of thin collagen fibrils that are parallel to the joint surface with inactive chondrocyte. The transitional zone (middle zone) is thicker than the superficial zone and formed of thicker collagen fibrils and spherical chondrocyte. In the deep zone, the collagen fibers are arranged vertical to the joint surface and the chondrocytes are spheroidal in shape. In the zone of calcified cartilage, the collagen fibrils are inserted into calcified cartilage, this zone provides a mechanical transition between cartilage and underlying bone as well as fixation between the 2 tissues. **(Newman, 1998)**

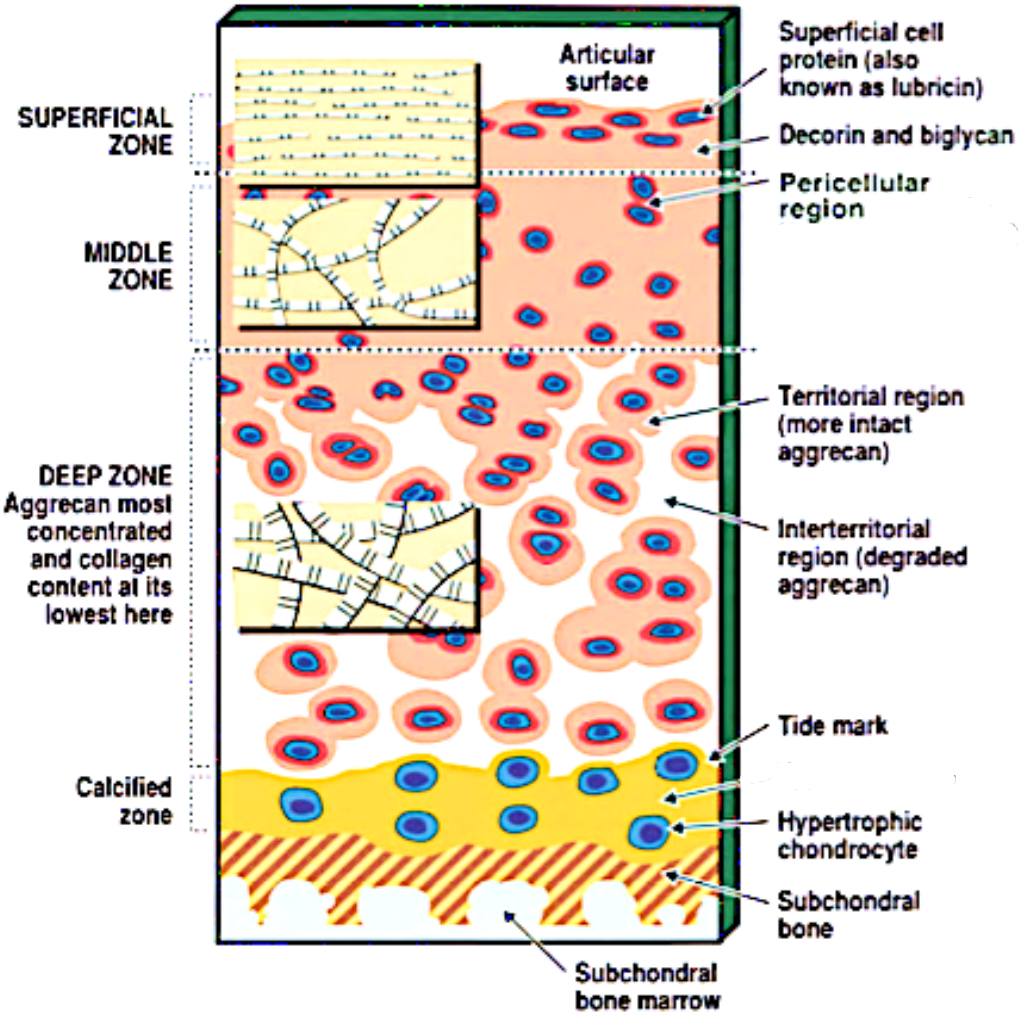



Figure 7 Diagrammatic drawing of adult human articular cartilage **(Peterson et al., 2000)**

## vi The Matrix

The matrix is divided into 3 regions, the first region is called the pericellular region (around chondrocytes) and is characterized by abundant proteoglycans and little collagen, while the second region is called the territorial region which surrounds the pericellular region and contains larger collagen fibrils that provide protection and cushioning to the cells, the third region is called the interterritorial region, in this region the collagen fibers are organized in a vertical manner that enable them to perform its mechanical function.

## 2.6 Body response to injury

The body responses to injuries in a very uniform way, although it differs from one organ or tissue to another, generally the process needs 2 essential components to be performed.

The first essential component is the cells that are capable of cleaning necrotic materials and form new tissues, either they arise in situ, migrate from nearby tissues or transferred to the injury site by blood vessels. The second essential component is the blood vessels, which deliver the needed cells and provide the proper biochemical environment that is needed for the healing response. **(Mankin H., 1982)**

Generally, the classic healing response in the body is divided into 3 phases, which are cell necrosis, inflammatory phase, and remodeling or reparative phase, and due to the fact that the cartilage is avascular tissue, therefore the cartilage response to injury differs from the classic response. The second limitation in the cartilage capability in healing is that the cartilage cells are imprisoned and trapped within the cartilage matrix and therefore are not capable of migration to the site of injury to promote the healing process. If the injury was deep enough to reach the subchondral bone, the body response will be nearly the same as the classic healing response. **(Mankin H., 1982)**

Thus, the type of response to cartilage injury will take one of two pathways, according to the depth of the injury which may be either superficial or deep. **(Falah et al., 2010)**

### i. Superficial (partial thickness) cartilage lesions

Adjacent to the area of injury, there is an area of necrosis with brief mitotic activity and matrix synthesis. But this activity rapidly ceases with no significant healing. **(Newman, 1998)**
However, studies have demonstrated that these lesions remain stable and rarely progress into osteoarthritis. **(Buckwalter JA et al. ,1988, Mankin H.J, 1982; Meachim G 1963)**

### ii. Deep (full- thickness) cartilage lesions

This occurs when the injury reaches the subchondral bone, the defect will be filled with fibrin clot which traps the cells from bone marrow. The inflammatory and reparative phases will produce a cellular mass, in which its deeper part facing the bone will reconstitute or reform the subchondral bone and the reparative tissue in the defect will undergo metaplasia to form fibrocartilage, the formed fibrocartilage resembles a cartilage scar and has lower biomechanical properties than the native hyaline cartilage. **(Shapiro et al., 1993)**

Within 2 weeks after the injury, the chondrocytes start to appear and produce collagen type II **(Buckwalter JA et al., 1988; Furukawa T., 1980)** and the proteoglycan content will decrease significantly and the collagen fibers of the superficial zone fail to appear. **(Mitchell N &Shepard N., 1976,1987)** This altered composition will affect the mechanical properties of the cartilage as stated by Furukawa et al. **(Furukawa T, 1980)** this might lead to vertical shear stresses between

the repair tissue and residual cartilage resulting in micromotion and degenerative changes which may appear early as 10 weeks after the injury.

Between 6 and 12 weeks the reformed matrix will be formed mainly of fibrocartilage and over time surface fibrillation and acellular areas will eventually appear due to the altered biomechanical properties. **(Newman, 1998)**

## 2.7 Methods of cartilage repair

Many methods were tried either on animals or clinical trials with variable degrees of success. These include shaving or debridement of the cartilage lesion, perforation of subchondral bones (abrasion arthroplasty, Pridie drilling, microfracture), transplantation of osteochondral grafts, perichondrium, periosteum, chondrocytes cell suspension and mesenchymal cells. Also, synthetic implants such as carbon fibers or biodegradable matrices and collagen gel were used to cover the lesions or as a carrier for chondrocytes or a growth stimulating factors. **(Newman, 1998)**

## 2.8 Classification of chondral and osteochondral lesions

Description of the cartilage lesions includes; localization of the lesion in the knee joint, either in medial femoral condyle (MFC), lateral femoral condyle (LFC), trochlea or patella, size of the lesion (in terms of surface area, small lesions $<2cm^2$, large lesions $> 2cm^2$), the shape of the lesion, containment of the lesion (surrounded by healthy tissues or not) and depth of the lesion. **(Browne & Branch, 2000) See tables 1-4.**

## 2.9 Diagnosis of cartilage lesions

The patients may suffer from gradual onset of pain with or without effusion, others may complain of acute onset of progressive pain with other symptoms as catching, locking or cracking.
In cases of patellar dislocation or dashboard injury where the possibility of the presence of loose bodies in the knee is high, the patient often complains of marked knee effusion and locking of the joint. **(Browne & Branch, 2000)**

### i. Physical examination of the knee

Routine knee examination should be performed to rule out malalignment, other causes of knee complaints such as instability of the knee after meniscal tears, ligamentous lesions or abnormalities in extensor mechanism. **(Browne & Branch, 2000; Craig W, 2003)**
Usually, the history and clinical examination will not provide all the information needed for the diagnosis of the cartilage lesions.

### ii. Radiological examination of the knee

This includes routine plain radiographs in anteroposterior (a.p.), lateral (lat.), axial views as well as long leg-axis x-ray. They may reveal changes in joint as joint narrowing, subchondral cysts or sclerosis that suggests osteoarthritic changes. Osteochondritis dissecans or some

ligamentous injuries can be also suspected in plain x-rays. The long leg-axis x-ray is required to measure the knee alignment (mechanical and anatomical axes of the knee) and it is recommended before performing any operative intervention to rule out any knee joint malalignment or deformities and to plan if a supplementary treatment is needed. **(Browne & Branch, 2000)**

MRI is the gold standard method for diagnosing knee problems including cartilage, ligamentous and meniscal lesions as well as bone bruises. Knee arthroscopy remains the most accurate method for diagnosing the cartilage lesions of the knee. **(Browne & Branch, 2000)**

Table 1 and Fig 8 Outerbridge classification

## (Outerbridge, 2001; Rodriguez-Merchan & Gomez-Cardero, 2010)

| Grade | Description |
|---|---|
| **G 0** | normal articular cartilage |
| **G I** | softening, blistering or swelling of the cartilage |
| **G II** | partial thickness fissures and clefts < 1cm in diameter |
| **G III** | full thickness fissures that reach subchondral bone > 1cm in diameter |
| **G IV** | exposed subchondral bone |

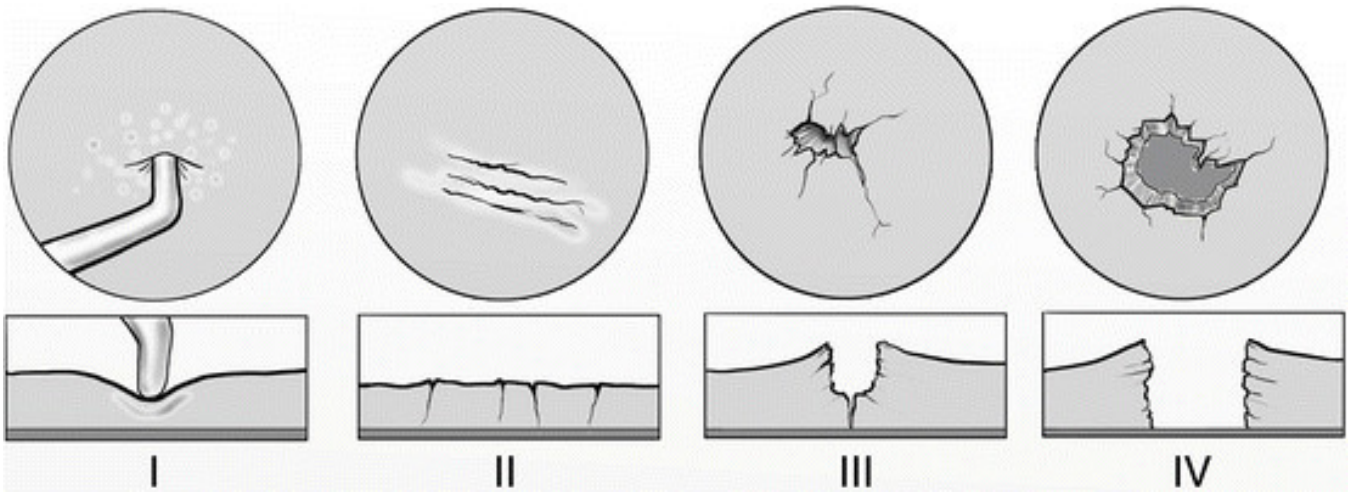



Figure 8 Grading of the cartilage lesions **(Kanakaris N.K., Lasanianos N.G., 2015)**

Table 2 International cartilage repair society (ICRS) classification **(van den Borne et al., 2007)**

| Grade | Description |
|---|---|
| **I** | superficial fissure |
| **II** | <50% depth loss |

| | |
|---|---|
| **III** | 50% to full thickness loss |
| **IV** | osteochondral lesion extends through the bone |
| **V** | osteochondritis dissecans (OCD) |
| **VI** | avascular necrosis |

Table 3 Bauer- Jackson descriptive classification:

**(Giurea M. et al., 1998)** From Grade I to Grade IV are acute traumatic lesions, Grade V and VI are degenerative lesions.

| Grade | Description |
|---|---|
| **I** | linear |
| **II** | stellate |
| **III** | chondral flap |
| **IV** | chondral crater |
| **V** | fibrillation |
| **VI** | exposed subchondral bone |

Table 4 Imhoff classification of OCL (osteochondral lesions)**,** 5 Grades

**(Imhoff A.B. et al, 2014)**

| Grade | X-ray | MRI | Arthroscope | Findings |
|---|---|---|---|---|
| **IA** | possible thinning of the bone | bone bruise, limited change in signal intensity in T1, edema in T2 | intact cartilage | bone contusion |
| **IB** | possible thinning of the bone | thickening of the cartilage | soft or uneven cartilage | cartilage softening |
| **IIA** | thinning of the bone | low signal intensity T1/T2, after i.v. contrast, increase T1 signal intensity | cartilage is demarcated but intact | demarcation without sclerosis, intact cartilage |
| **IIB** | thinning of the bone (demarcation by sclerosis) | same as IIA, but no change in signal intensity after i.v. contrast material injection | same as IIA | demarcation with sclerosis, intact cartilage |
| **IIIA** | partially loose fragment | low signal intensity T1/T2, increase T2 signal intensity after i.v. contrast | partial loose fragment, cartilage is intact | partial loose and vital fragment, cartilage intact, no sclerosis |

| | | | | |
|---|---|---|---|---|
| **IIIB** | partially loose fragment, sclerosis zone | same as IIIA but with no increase in signal intensity | partial loose fragment, cartilage is not intact | partial loose and non-vital fragment, cartilage isn't intact, marked sclerosis |
| **IVA** | complete loose fragment with or without dislocation | high subchondral signal intensity, increase signal intensity after i.v. contrast material injection. | OCD | vital fragment, no sclerosis |
| **IVB** | complete loose fragment with or without dislocation | same as VA but no increase signal intensity after i.v. contrast material injection | OCD | non-vital fragment, marked sclerosis |
| **VA** | cystic bony changes, no sclerosis | high signal intensity T2 | cartilage intact or chondromalacia | cyst without sclerosis |
| **VB** | cystic bony changes, with sclerosis | low Signal intensity T1/T2 | same as VA | cyst with sclerosis |

# 3 Aim of the work

Our study aimed to evaluate the clinical and radiological results of treating the large multilocular full thickness cartilage lesions of the knee joint by matrix autologous chondrocyte transplantation and to prove to which extent the following hypothesis are right.

1) The use of cell-based biological approach (MACT) is an efficient method for the treatment of multilocular large sized full thickness cartilage lesions of the knee.
2) The evaluation of the subjective and objective results of the treatment of multilocular large full thickness cartilage defects in the knee joint by using MACT.
3) The evaluation of the significance of the MACT in the treatment of the cartilage lesions.
4) The identification of individual criteria that influence the postoperative outcome.

# 4 Patients and Methods

## 4.1 Indications

The indication of MACT is established after detailed clinical examination at the outpatient clinic and radiological examination. The decision is discussed and taken together with the patient after discussing all the available treatment options, possible complications and postoperative rehabilitation.

Arthroscopy of the knee is done as a first step in this technique. The lesion size is measured in terms of surface area and depth and documented. Other concomitant pathologies of the knee is diagnosed and treated accordingly when needed. **(Outerbridge, 1961)**

The use of MACT is indicated in grade III to grade IV according to Outerbridge classification. This technique is indicated in large cartilage defects, from lesions larger than 2 $cm^2$ and up to 14 $cm^2$. It is important here to mention that having an intact meniscus or at least 2/3 of the meniscus and straight leg axis are important prerequisites for the success of this procedure.

Contraindications to this procedure include advanced osteoarthritis, kissing cartilage lesions, inflammatory joint disease and neurological lesions that will prevent the adequate postoperative rehabilitation program. Relative contraindications include subtotal meniscectomy (more than 2/3 of the meniscus is removed), knee instability and malalignment.

### MACT 3D-Construct (Novocart ® 3D)

The membrane implanted in our patients was provided from the company TETEC® (Reutlingen-Germany).

The membrane is a combination of autologous cartilage cells implanted on three-dimensional collagen-based matrix. The use of Novocart ® 3D is recommended in large circumscribed cartilage lesions and they are individually manufactured for each patient.

**Description:**
Novocart® 3D is a collagen-based membrane with endogenous cartilage cells on a high-quality substrate. The patient's own cultured chondrocytes are distributed on the matrix that will be implanted in the defect via a mini-arthrotomy.

Cell cultivation takes place in a certified laboratory and clean rooms. This is done in the special laboratory of the company TETEC AG on a special matrix that achieves physiological cell distribution and simplifies implantation.

The implantation of the membrane with the proliferated cells into the cartilage defect takes place after 3 weeks.

The membrane consists of 2 different surfaces. The cell-free surface, which is tough and tear resistant, this surface faces the joint cavity and prevents the entry of nonspecific cells from the synovial fluid into the matrix tissue in order to prevent the formation of mixed tissues inside the defect as well as preventing the escape of the implanted chondrocyte from the inner surface facing the cartilage defect. The second surface of the membrane is called the cell-bearing surface that contains the cultivated cells and will face the defect.

The transplanted cartilage cells, therefore, must be capable of synthesizing the matrix components in order to produce cartilage tissue which has nearly the same biomechanical properties as native cartilage.

Through using the isolation and cultivation technique developed by the company TETEC, it is possible to cultivate cartilage cells that are capable of production of type II collagen, Aggrecan and cartilage-relevant growth factors such as BMP-2 (bone morphogenic protein-2) and proteins. **(http://www.tetec-ag.de/cps/rde/xchg/cw-tetec-de-int/hs.xsl/7321.html)**

The membrane is transported is placed on a polyethylene plate with a metallic frame and stored in a sterile sealed container to the hospital. **Fig. 9,10**


Figure 9 The membrane in its transport sealed container

Figure 10 The membrane in its metallic frame before transplantation

## 4.2 Inclusion and exclusion criteria

### Inclusion criteria:

- Young and middle-aged patients (less than 45 years old),
- contained full-thickness cartilage defects,
- big sized lesions with surface area more than 2 $cm^2$,
- lesions not involving injury to the subchondral bone,
- at least 2/3 of the meniscus size is remaining.

### Exclusion criteria:

- Kissing cartilage lesions,
- developed osteoarthritis,
- inflammatory articular disease or septic arthritis,
- chronic inflammatory joint diseases like Rheumatoid arthritis or Gouty arthritis,
- patients undergoing immunosuppressive treatment as well as patients suffering from malignancy,
- patients with neuromuscular disorders that prevent them from performing the postoperative rehabilitation program.

## 4.3 Surgical technique **(Imhoff et al., 2017) Fig. 12-13**

After fulfilling the inclusions criteria, the indication of the therapy is made, the patients undergone the procedures; the operative technique consists of 2 steps; the first step is done arthroscopically, to confirm the diagnosis and to measure the exact size, site, depth and grade of the lesions, as well as initial treatment of co-existing knee disease. In defects less than 10 $cm^2$ only two cartilaginous bony cylinders are harvested from the intercondylar notch (medial rim of the trochlea) of the knee by hollow punches of 4 mm diameter from outside the weight-bearing zone (approximate depth 7-8 mm). In the defects that are larger than 10 $cm^2$, 3 cylinders should be harvested in order to obtain sufficient chondrocytes. A total of 75-300 mg of cartilaginous tissue were obtained. The harvested samples were then preserved in a transport vial containing a sterile nutrient solution. **Fig. 11.**

After that, the cylinders are sent to the laboratory under sterile measures where the chondrocytes are mechanically and enzymatically isolated from the harvested samples.

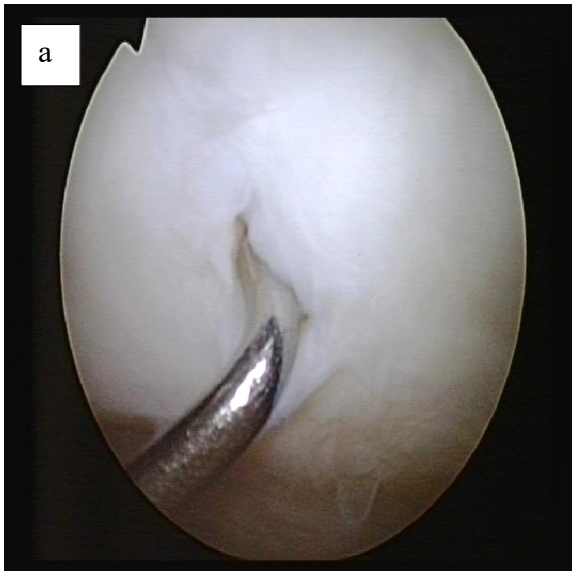
The first step in the isolation process is the separation of the cartilaginous part from the bone by a scalpel. The separated cartilage will be then impregnated in collagenase for 8 hours to allow the enzymatic separation of cartilage from remnants of underlying bone.

Subsequently, the chondrocytes were cultured in a cell culture flask for about two to three weeks for cell proliferation. After cell proliferation, the chondrocytes are applied uniformly as a cell suspension over the collagen membrane.

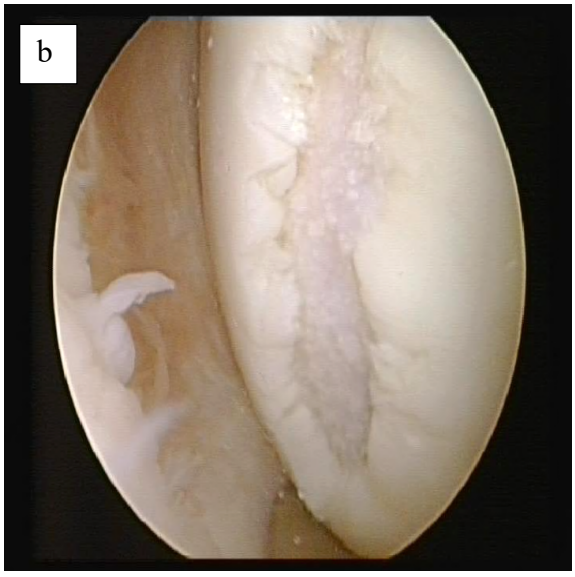
The surface area of a single matrix is about 10 $cm^2$. For defects with a total size more than 10 $cm^2$, two matrices were supplied to be sufficient to cover the defects.


Figure 11 The nutrient container

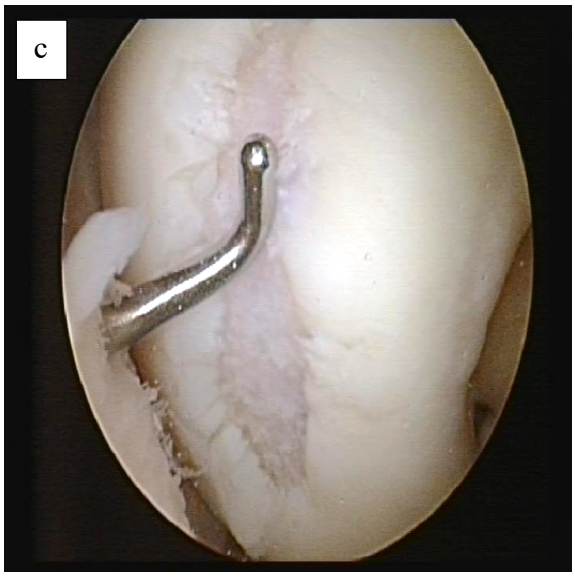
Figure 12 Arthroscopic images of the first step of the procedure

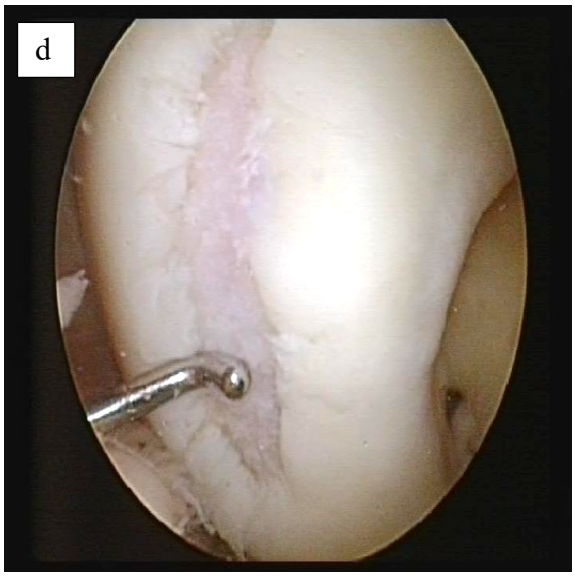



a- Arthroscopic examination the cartilage

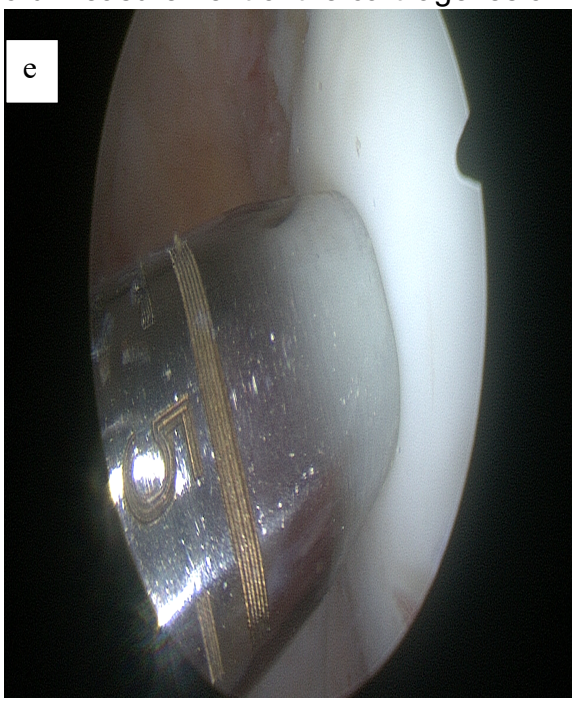


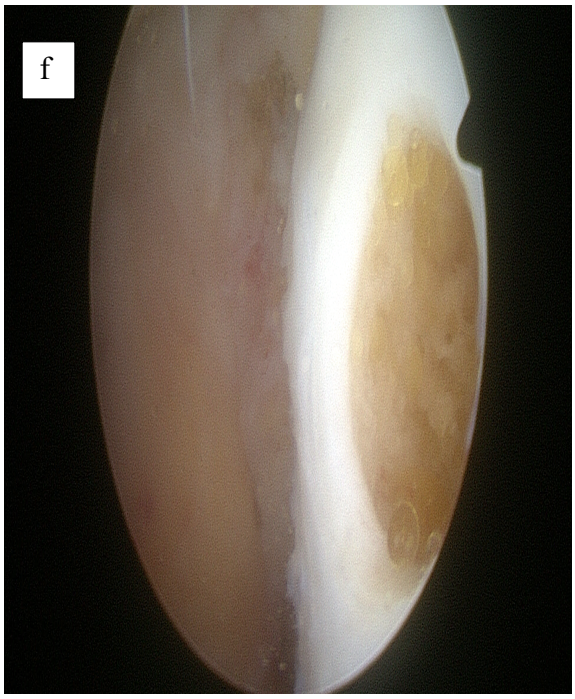

b- Diagnosis of cartilage lesion




c-d Measurement of the cartilage lesion




e- Harvesting the cartilage samples

f- After harvesting the cartilage samples

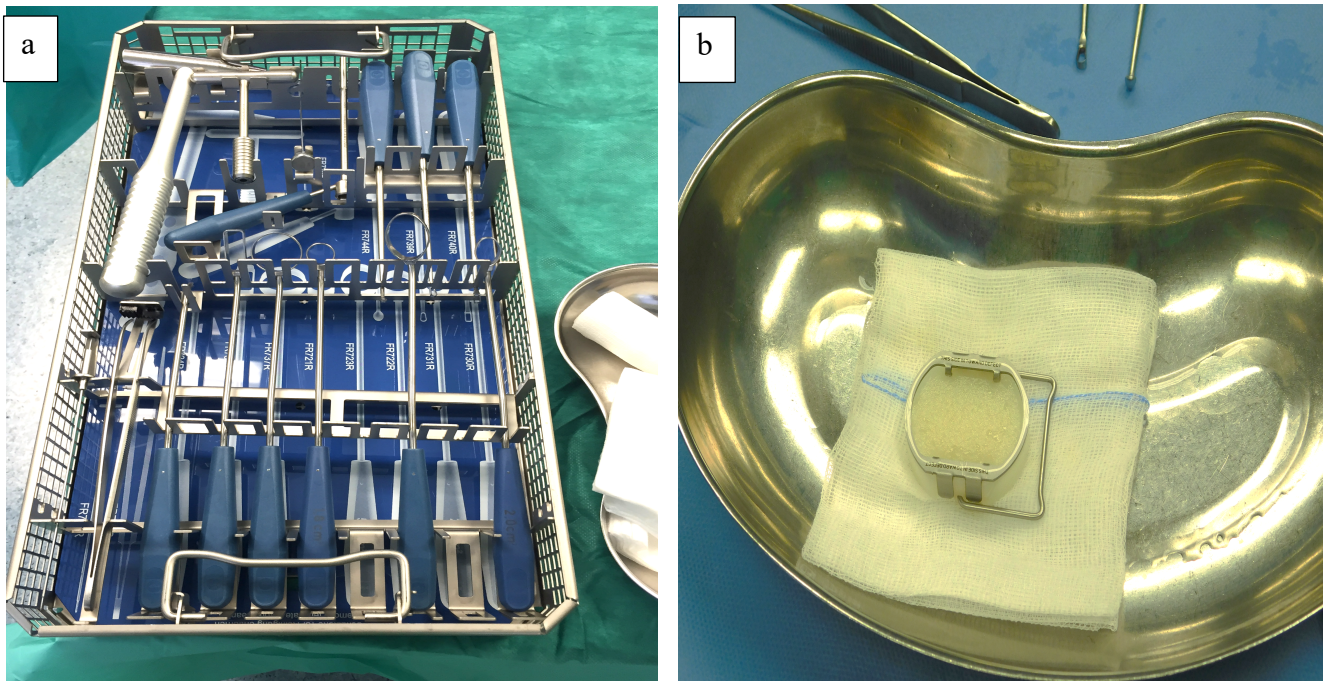



Figure 13 a, b Instruments' set used in the second step of the procedure, graft in its metallic container

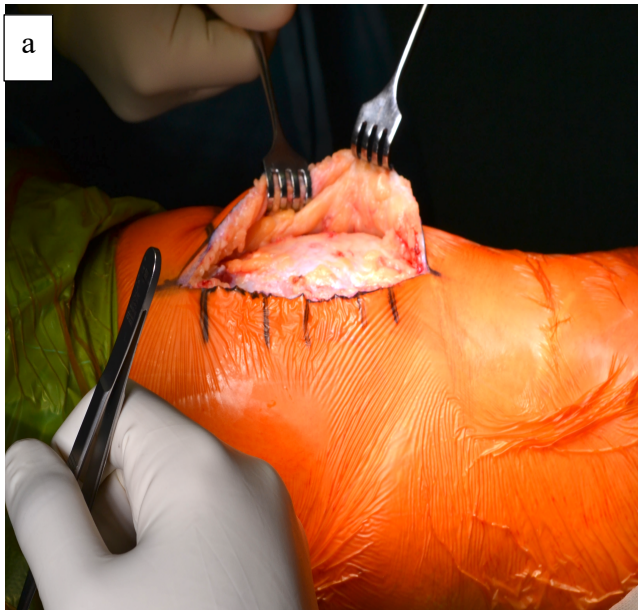
After 2-3 weeks, the second step of the procedure takes place, and the collagen membrane with the cells are implanted into the defect.

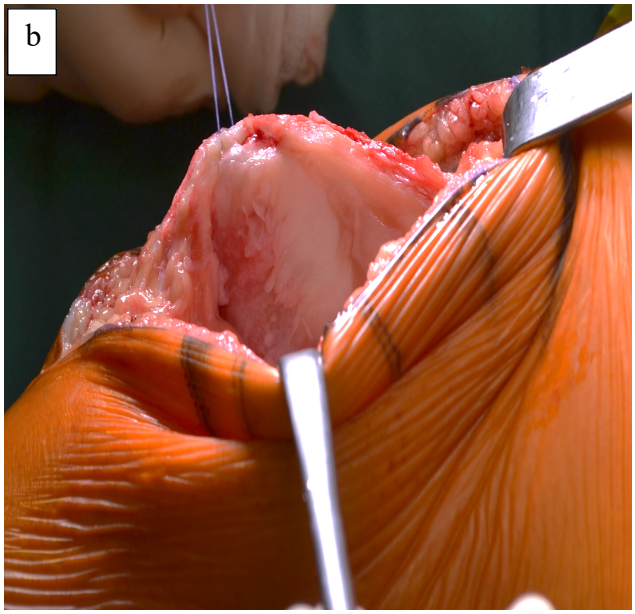
This is done by means of parapatellar arthrotomy to expose the defect. Debridement of the cartilage defect with a special curette **(Fig. 14)** till reaching the subchondral bone.

The fixation of the implant is done by Polydioxanone absorbable sutures (PDS 6,0) into the surrounding healthy cartilage tissue.

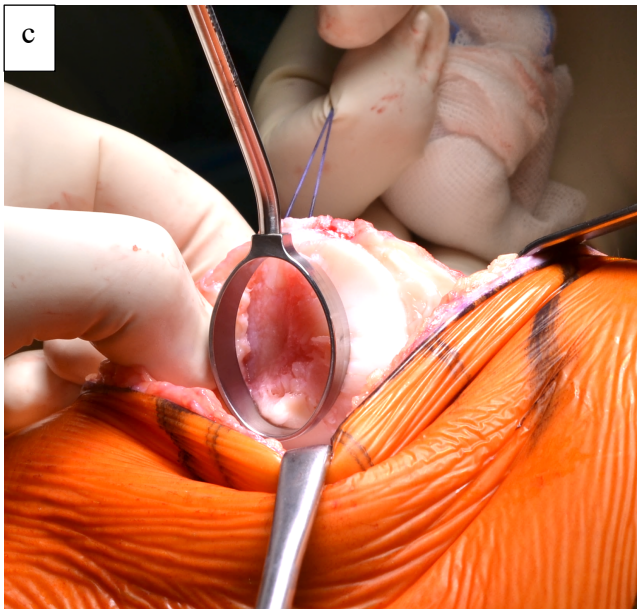
After fixation of the membrane, a drain (without suction) is inserted into the knee followed by closure of the wound. The drain is removed usually after 1-2 days. Skin stitches are removed after 12-14 days after the operation.

Figure 14 a - k The 2nd step of the operation

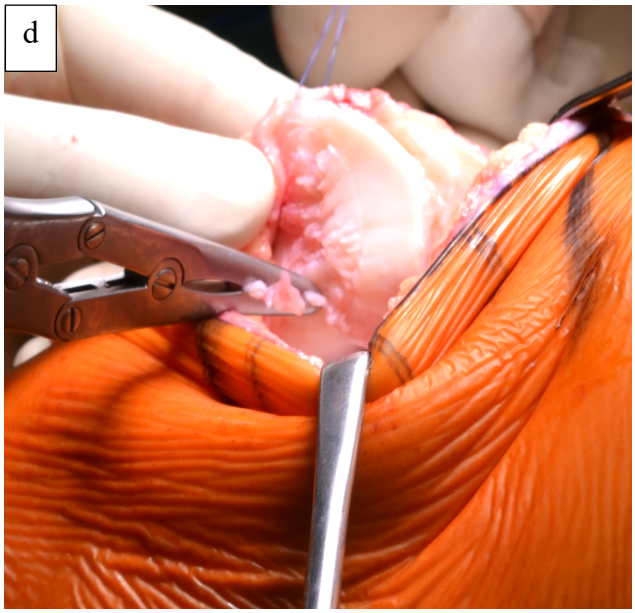


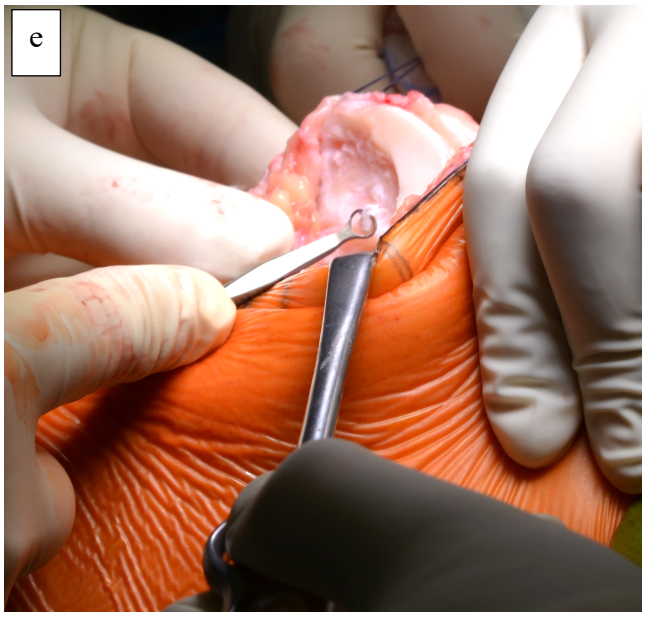

a-b The cartilage defect is exposed through a parapatellar incision, then exposure of the cartilage lesion accordingly.




c- Measurement of the cartilage lesion with a template (the templates are available with different sizes in the instrument set)

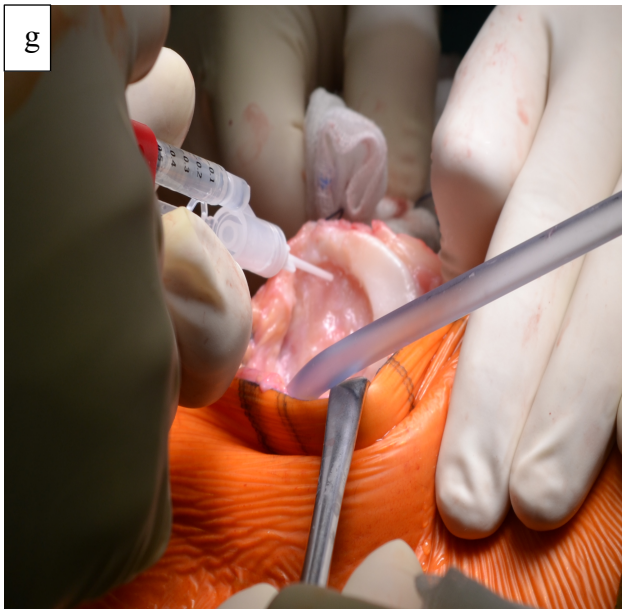



d- Cartilage lesion debridement

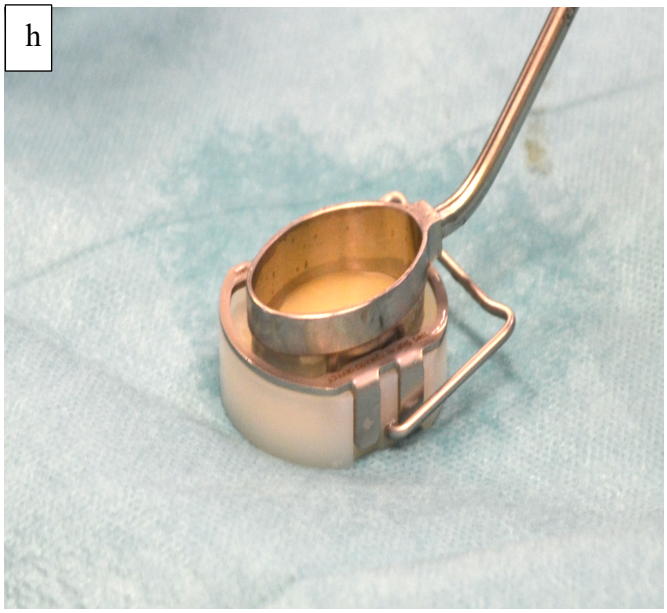



e-Cartilage lesion debridement with special curette

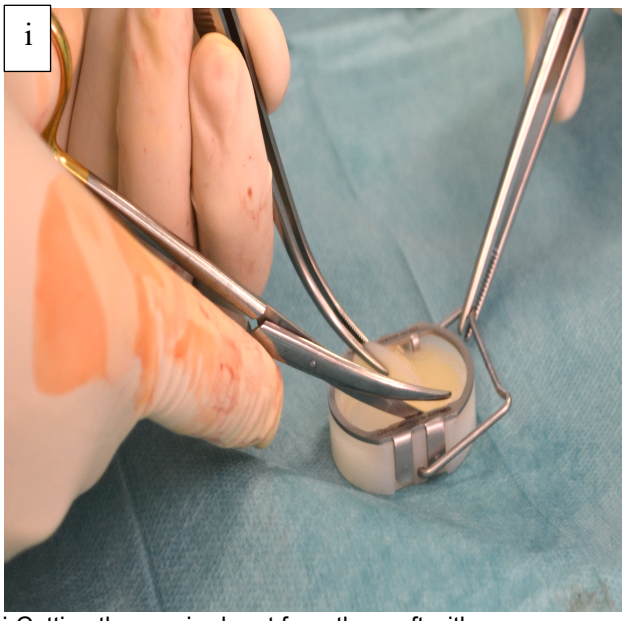

f- Final picture after lesion debridement



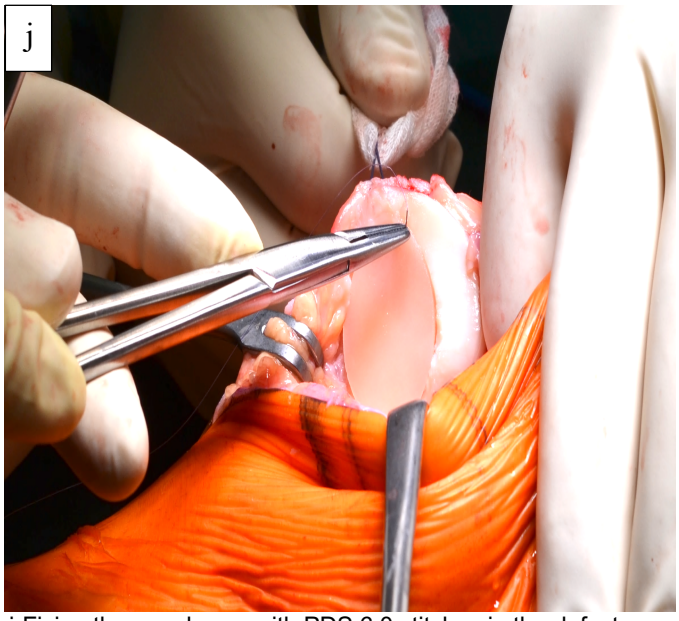

g- Application of fibrin glue in the lesion area



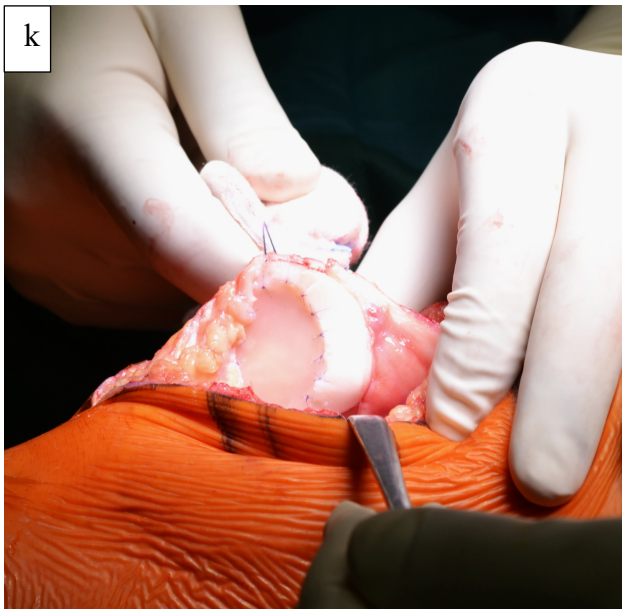

h- Marking the membrane with the template




i-Cutting the required part from the graft with a scissor after selecting the size




j-Fixing the membrane with PDS 6.0 stitches in the defect area




k- Final picture after membrane fixation

## 4.4 Postoperative treatment protocol **(Imhoff A.B., 2017)**

Postoperative Rehabilitation program consists of 4 phases and differs according to the site of the cartilage lesion:

Bed rest for 48 hours. Using the CPM from the second postoperative day as well as beginning of the physiotherapy.
**Range of motion and weight bearing:** From 1st to 6th postoperative weeks: No weight bearing is allowed.
The range of motion is dependent on the localization of the defect.
In defects of the femoral condyles, no limitation of movement is required, but in defects of the patella, the flexion is limited to 30° (1st 2 weeks), 60° (3rd-4th week), 90° (5th-6th week).

From the 7th postoperative week, gradual weight bearing is allowed with a rate of 20kg/ week and according the follow up and knee status, the range of motion in case of patellar lesions is also increased.

## 4.5 Statistical methods

The statistical analysis of the collected data was carried out using the statistical program SPSS (version 23). The descriptive data were presented with mean and standard deviation. The analysis was then used to examine the relationship between all potential influencing factors for the clinical and radiological outcome postoperatively. To determine significant differences between preoperative and postoperative IKDC (International Knee Documentation Committee) results, the Mann-Whitney-U/ Chi-square test were used in comparisons between two groups at a time. All test methods used are non-parametric tests, which were chosen due to the low number of patients. For all calculations with an error probability of less than 5% ($p < 0.05$), the result was considered significant.

# Scores used for assessment of the patients

Each patient was clinically examined, and the findings were documented on an examination sheet. All the patients filled out a standardized questionnaire, consisting of several parts. The following scores were used to evaluate the subjective and objective examination findings: VAS (Visual Analogue Scale), IKDC (International Knee Documentation Committee) score, Tegner activity scale, KOOS (Knee injury and Osteoarthritis Outcome Score), and Lysholm scores.

## Overall assessment

At the postoperative follow-up, the patients were contacted and examined in the period between October 2014 to March 2016. The patients were questioned about the overall assessment of the treatment, in regard to satisfaction and return to preoperative activity and sport's levels. The patient's satisfaction was classified into "very satisfied", "satisfied" and "not satisfied".

Patients who agreed to join the study were invited to postoperative physical examination as well as radiological examination if indicated. The physical findings were recorded on the examination sheet and the MRI images were evaluated and the MOCART score was calculated (Magnetic Resonance Observation of Cartilage Repair Tissue) through our colleagues in the radiology department in Klinikum rechts der Isar.

## i VAS (Visual Analogue Scale) **(Hawker et al., 2011)**

For the documentation of pain, VAS (visual analog scale) was used.
The patients marked the perceived pain intensity on a 100-mm line, with the beginning of the line showing no pain (0) and the end of the line the strongest non-bearable pain (100).

In the evaluation, the distance between the 0 point and the patient's mark was measured. The measurement result was expressed in millimeters and matched with the estimated pain intensity.


Figure 15 VAS (Visual Analogue Scale)

## ii IKDC (International Knee Documentation Committee) scale **(Rossi et al., 2002)**

As an evaluation base of the subjective and objective clinical parameters, the "2000 International Knee Documentation Committee IKDC " questionnaire was used.
The IKDC consists of 18 items. The patient should choose only one answer for each question, each answer has corresponding points, these points would be summed at the end. The maximum sum of the evaluated questions and its corresponding answers is 87, which means. The best result.

For a better overview, this sum is expressed into a percentage through a special equation, which reflects the relative knee function. A score of 87 is interpreted to mean no limitation of daily living or sports activities as well as the absence of symptoms.

1. **What is the highest level of activity that you can perform without significant knee pain?**

4 ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer.
3 ☐ Strenuous activities like heavy physical work, skiing or tennis.
2 ☐ Moderate activities like moderate physical work, running or jogging.
1 ☐ Light activities like walking, housework or yard work.
0 ☐ Unable to perform any of the above activities due to knee pain.

**2. During the past 4 weeks, or since your injury, how often have you experienced pain?**

never 0 1 2 3 4 5 6 7 8 9 10 constant
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**3. If you have pain, how severe is it?**

**no pain** 0 1 2 3 4 5 6 7 8 9 10 **worst pain imaginable**

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**4. During the last 4 weeks or since your injury how stiff or swollen was your knee?**
4 ☐ No swelling.
3 ☐ Mild.
2 ☐ Moderate.
1 ☐ Very.
0 ☐ Extreme.

**5. What is the highest level of activity you can perform without significant swelling in your knees?**
4 ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer.
3 ☐ strenuous activities like heavy physical work, skiing, or tennis.
2 ☐ Moderate activities like moderate physical work, running or jogging.
1 ☐ Light activities like walking, housework, or yard work.
0 ☐ Unable to perform any of the above activities due to knee swelling.

**6. During the last 4 weeks or since your injury, did your knee catch or lock?**
1 ☐ Yes.
0 ☐ No.

**7. What is the highest level of activity that you can do without giving way in your knee?**
4 ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer.
3 ☐ Strenuous activities like heavy physical work, skiing, or tennis.
2 ☐ Moderate activities like moderate physical work, running or jogging.
1 ☐ Light activities like walking, housework, or yard work.
0 ☐ Unable to perform any of the above activities due to knee swelling.

## Sports activities

**8. What is the highest level of activity you can participate in on regular basis?**

4 ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer.
3 ☐ Strenuous activities like heavy physical work, skiing, or tennis.
2 ☐ Moderate activities like moderate physical work, running or jogging.
1 ☐ Light activities like walking, housework, or yard work.
0 ☐ Unable to perform any of the above activities due to knee swelling.

**9. How does your knee affect your ability to?**

a. Go upstairs
4 ☐ No difficulty.
3 ☐ Minimal difficulty.
2 ☐ Moderate difficulty.
1 ☐ Extreme difficulty.
0 ☐ Unable to do.

b. Go downstairs
4 ☐ No difficulty.
3 ☐ Minimal difficulty.
2 ☐ Moderate difficulty.
1 ☐ Extreme difficulty.
0 ☐ Unable to do.

c. Kneeling:
4 ☐ No difficulty.
3 ☐ Minimal difficulty.
2 ☐ Moderate difficulty.
1 ☐ Extreme difficulty.
0 ☐ Unable to do.

d. Squat:
4 ☐ No difficulty.
3 ☐ Minimal difficulty.
2 ☐ Moderate difficulty.
1 ☐ Extreme difficulty.
0 ☐ Unable to do.

e. Sit with bending your knee:
4 ☐ No difficulty.

3 ☐ Minimal difficulty.
2☐ Moderate difficulty.
1 ☐ Extreme difficulty.
0 ☐ Unable to do.

f. Rise from a chair:
4 ☐ No difficulty.
3 ☐ Minimal difficulty.
2 ☐ Moderate difficulty.
1 ☐ Extreme difficulty.
0 ☐ Unable to do.

g. Run straight ahead:
4 ☐ No difficulty.
3 ☐ Minimal difficulty.
2 ☐ Moderate difficulty.
1 ☐ Extreme difficulty.
0 ☐ Unable to do.

h. Jump and land on your injured leg:
4 ☐ No difficulty.
3 ☐ Minimal difficulty.
2 ☐ Moderate difficulty.
1 ☐ Extreme difficulty.
0 ☐ Unable to do.

i. Quick stop and go movements:
4 ☐ No difficulty.
3 ☐ Minimal difficulty.
2 ☐ Moderate difficulty.
1 ☐ Extreme difficulty.
0 ☐ Unable to do.

**Function, and activity of daily living -** The following questions concern your physical function when you are active. The questions should be answered with regard to the degree of difficulty that you have experienced during the **last week** due to your knee problem.

**10. How would you rate the function of your knee on a scale from 0 to 10, regarding that 10 is normal, excellent function and 0 is the inability to perform any of your all daily activities (ADL) which may include sports?**

a- Function prior to your knee injury:

**can't perform ADL** ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 **no limitation of ADL**

b- Current function of your knee:

**cannot perform ADL** ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 **no limitation of ADL**

The (IKDC subjective knee evaluation form) is calculated by summing the scores for the individual items and then transforming the score to a scale that ranges from 0 to 100.

- In the Items no. 2 and 3 the best score is 0 and the lowest score is 10.
- In the item number 6: **No** corresponds to 0 and it is the best score, while **yes** corresponds to 1 and it is the worst score in this item.
- In item no. 10, 10a is not included in overall score and in 10b the best score is 10 and the lowest score is zero
- In the other items the best score is 4 and the lowest is 0

**IKDC scale =**

$$\frac{sum\ of\ items}{maximum\ possible\ score\ (according\ to\ the\ no.of\ answered\ questions=87)} \times 100$$

To calculate the IKDC scale, simply add the score for each item (the smallest number by each item checked) and divide by the maximum possible score which is 87 and multiply by 100.

The IKDC subjective knee form score can only be calculated when there are responses to at least 90% of the items (i.e. when responses have been provided for at least 16 items).

Figure 16 Grouping of the patients according to IKDC (Group grades from A to D)

**2000**
**IKDC KNEE EXAMINATION FORM**

**Patient Name:**_____ **Date of Birth:**_____/_____/_____ (Day / Month / Year)

**Gender:** ☐F ☐M **Age:**_____ **Date of Examination:**_____/_____/_____ (Day / Month / Year)

| | | | | |
|---|---|---|---|---|
| **Generalized Laxity:** | ☐light | ☐normal | ☐lax | |
| **Alignment:** | ☐obvious varus | ☐normal | ☐obvious valgus | |
| **Patella Position:** | ☐obvious baja | ☐normal | ☐obvious alta | |
| **Patella Subluxation/Dislocation:** | ☐centered | ☐subluxable | ☐subluxed | ☐dislocated |
| **Range of Motion (Ext/Flex):** | Index Side: passive_____/_____/_____ | | active_____/_____/_____ | |
| | Opposite Side: passive_____/_____/_____ | | active_____/_____/_____ | |

| SEVEN GROUPS | FOUR GRADES A Normal | B Nearly Normal | C Abnormal | D Severely Abnormal | *Group Grade A | B | C | D |
|---|---|---|---|---|---|---|---|---|
| **1. Effusion** | ☐None | ☐Mild | ☐Moderate | ☐Severe | ☐ | ☐ | ☐ | ☐ |
| **2. Passive Motion Deficit** | | | | | | | | |
| ΔLack of extension | ☐< 3° | ☐3 to 5° | ☐6 to 10° | ☐> 10° | | | | |
| ΔLack of flexion | ☐0 to 5° | ☐6 to 15° | ☐16 to 25° | ☐> 25° | ☐ | ☐ | ☐ | ☐ |
| **3. Ligament Examination** (manual, instrumented, x-ray) | | | | | | | | |
| ΔLachman (25° flex) (134N) | ☐+1 to 2mm | ☐3 to 5mm (1+) ☐< -1 to –3 | ☐6 to 10mm (2+) ☐< -3 stiff | ☐> 10mm (3+) | | | | |
| ΔLachman (25° flex) manual max | ☐+1 to 2mm | ☐3 to 5mm | ☐6 to 10mm | ☐> 10mm | | | | |
| Anterior endpoint: | ☐firm | | ☐soft | | | | | |
| ΔTotal AP Translation (25° flex) | ☐0 to 2mm | ☐3 to 5mm | ☐6 to 10mm | ☐> 10mm | | | | |
| ΔTotal AP Translation (70° flex) | ☐0 to 2mm | ☐3 to 5mm | ☐6 to 10mm | ☐> 10mm | | | | |
| ΔPosterior Drawer Test (70° flex) | ☐0 to 2mm | ☐3 to 5mm | ☐6 to 10mm | ☐> 10mm | | | | |
| ΔMed Joint Opening (20° flex/valgus rot) | ☐0 to 2mm | ☐3 to 5mm | ☐6 to 10mm | ☐> 10mm | | | | |
| ΔLat Joint Opening (20° flex/varus rot) | ☐0 to 2mm | ☐3 to 5mm | ☐6 to 10mm | ☐> 10mm | | | | |
| ΔExternal Rotation Test (30° flex prone) | ☐< 5° | ☐6 to 10° | ☐11 to 19° | ☐> 20° | | | | |
| ΔExternal Rotation Test (90° flex prone) | ☐< 5° | ☐6 to 10° | ☐11 to 19° | ☐> 20° | | | | |
| ΔPivot Shift | ☐equal | ☐+ glide | ☐+ + (clunk) | ☐+ + + (gross) | | | | |
| ΔReverse Pivot Shift | ☐equal | ☐glide | ☐gross | ☐marked | | | | |
| | | | | | ☐ | ☐ | ☐ | ☐ |
| **4. Compartment Findings** | | | crepitation with | | | | | |
| ΔCrepitus Ant. Compartment | ☐none | ☐moderate | ☐mild pain | ☐> mild pain | | | | |
| ΔCrepitus Med. Compartment | ☐none | ☐moderate | ☐mild pain | ☐> mild pain | | | | |
| ΔCrepitus Lat. Compartment | ☐none | ☐moderate | ☐mild pain | ☐> mild pain | | | | |
| **5. Harvest Site Pathology** | ☐none | ☐mild | ☐moderate | ☐severe | | | | |
| **6. X-ray Findings** | | | | | | | | |
| Med. Joint Space | ☐none | ☐mild | ☐moderate | ☐severe | | | | |
| Lat. Joint Space | ☐none | ☐mild | ☐moderate | ☐severe | | | | |
| Patellofemoral | ☐none | ☐mild | ☐moderate | ☐severe | | | | |
| Ant. Joint Space (sagittal) | ☐none | ☐mild | ☐moderate | ☐severe | | | | |
| Post. Joint Space (sagittal) | ☐none | ☐mild | ☐moderate | ☐severe | | | | |
| **7. Functional Test** | | | | | | | | |
| One Leg Hop (% of opposite side) | ☐≥ 90% | ☐89 to 76% | ☐75 to 50% | ☐< 50% | | | | |
| ****Final Evaluation** | | | | | ☐ | ☐ | ☐ | ☐ |

* Group grade: The lowest grade within a group determines the group grade
** Final evaluation: the worst group grade determines the final evaluation for acute and subacute patients. For chronic patients compare preoperative and postoperative evaluations. In a final evaluation only the first 3 groups are evaluated but all groups must be documented. Δ Difference in involved knee compared to normal or what is assumed to be normal.

**IKDC COMMITTEE** AOSSM: Anderson, A., Bergfeld, J., Boland, A. Dye, S., Feagin, J., Harner, C. Mohtadi, N. Richmond, J. Shelbourne, D., Terry, G. ESSKA: Staubli, H., Hefti, F., Hoher, J., Jacob, R., Mueller, W., Neyret, P. APOSSM: Chan, K., Kurosaka, M.

### iii Tegner activity scale **(Briggs et al., 2009)**

It is a scale formed of list of activities of daily living, sports, recreation and competitive sports. The patients are asked to describe the best activity level before and after the treatment. It varies from 0-10, 0 represents sick leave or disabilities due to knee problems, 10 represents the participation in sports at national and international levels.

Table 5 Tegner activity scale (**Briggs et al., 2009)**

| | |
|---|---|
| **Level 10** | competitive sports as soccer, football, rugby (national elite) |
| **Level 9** | competitive sports as soccer, football, rugby (lower divisions), ice hockey, wrestling, gymnastics, basketball |
| **Level 8** | competitive sports as racquetball, squash or badminton, track and field athletics (jumping, etc.), downhill skiing |
| **Level 7** | competitive sports as tennis, running, motorcars speedway, handball, recreational sports as soccer, football, rugby, ice hockey, basketball, squash, racquetball, running, dancing |
| **Level 6** | recreational sports as tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week |
| **Level 5** | heavy work (construction, etc.), competitive sports as cycling, cross-country skiing. Recreational sports as jogging on uneven ground at least twice weekly |
| **Level 4** | moderate work (e.g. truck driving, etc.) |
| **Level 3** | light work |
| **Level 2** | light work, walking on uneven ground possible, but impossible to hike |
| **Level 1** | sedentary work |
| **Level 0** | sick leave or disability pension because of knee problems |

### iv Knee Injury and Osteoarthritis Outcome Score (KOOS) **(Collins et al., 2011)**

It consists of 5 subscales: symptoms (7 items), pain (9 items), activities of daily living (ADL, 17 items), sport and recreation function (Sport/Rec, 5 items) and knee-related quality of life (QOL, 4 items). The questionnaire targets the week before answering it. Standardized answer options are given (5 boxes) and each question is assigned a score from 0 (no problems) to 4 (extreme problems). A score of 100 indicating no symptoms and 0 indicating extreme symptoms. Each of the 5 subscales is calculated by adding the items included together.

**Interpretation of the score:** the added points are transformed to a scale, 0 corresponds to extreme knee problems, and 100 responds to no knee problems.

**Assign the following scores to the boxes:**

- None = 0
- Mild = 1
- Moderate = 2
- Severe = 3
- Extreme = 4

Each subscale score is calculated independently. Calculate the mean score of the individual items of each subscale and divide them by 4 (the highest possible score for a single answer option). 100 indicates no problems and 0 indicates extreme problems.

**Symptoms: (S)**
These questions should be answered thinking of your knee symptoms during the last week.

**S1. Do you have swelling in your knee?**
☐ Never.
☐ Rarely.
☐ Sometimes.
☐ Often.
☐ Always.

**S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?**
☐ Never.
☐ Rarely.
☐ Sometimes.
☐ Often.
☐ Always.

**S3. Does your knee catch or locked when moving?**
☐ Never.
☐ Rarely.
☐ Sometimes.
☐ Often.
☐ Always.

**S4. Can you straighten your knee fully?**
☐ Always.
☐ Often.
☐ Sometimes.
☐ Rarely.
☐ Never.

**S5. Can you bend your knee fully?**
☐ Always.
☐ Often.
☐ Sometimes.
☐ Rarely.
☐ Never.

**Stiffness**

The following questions concern the amount of joint stiffness that you have experienced during the last week in your knee. Stiffness is a sensation of restriction or slowness in the ease of movements in your knee joint.

**S6. How severe is your knee joint stiffness after awakening in the morning?**

☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**S7. How severe is your knee stiffness after sitting, lying or resting later in the day?**

☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**Pain: (P)**

**P1. How often do you experience knee pain?**

☐ Never.
☐ Monthly.
☐ Weekly.
☐ Daily.
☐ Always.

**How much did your knee hurt in the last week during the following activities?**

**P2. Twisting/pivoting?**

☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**P3. Straightening knee fully?**

☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**P4. Bending knee fully?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**P5. Walking on flat surface?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**P6. Going up or down stairs?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**P7. At night while in bed?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**P8. Sitting or lying?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**P9. Standing upright?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**Function, daily living: (ADL)**

The following questions concern your physical function. This means your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

**A1. Descending stairs?**

☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A2. Ascending stairs?**

☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A3. Rising from sitting?**

☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A4. Standing?**

☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A5. Bending to floor/ pick up an object?**

☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A6. Walking on flat surface?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A7. Getting in/ out of the car?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A8. Going shopping?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A9. Putting on socks/stockings?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A10. Rising from bed?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A11. Taking off socks/ stockings?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A12. Lying in bed (turning over, maintaining knee position)?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A13. Getting in/ out of bath?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A14. Sitting?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A15. Getting on/off toilet?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc.)?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**A17. Light domestic duties (cooking, dusting, etc.)?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**Sport and recreation function:**

**SP1. Squatting?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**SP2. Running?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**SP3. Jumping?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**SP4. Twisting/pivoting on your injured knee?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**SP5. Kneeling?**
☐ None.
☐ Mild.
☐ Moderate.
☐ Severe.
☐ Extreme.

**Quality of Life: (QOL)**

**Q1. How often are you aware of your knee problem?**
☐ Never.
☐ Monthly.
☐ Weekly.
☐ Daily.
☐ Constantly.

**Q2. Have you modified your lifestyle to avoid potentially damaging/ painful activities to your knee?**
☐ Not at all.
☐ Mildly.
☐ Moderately.
☐ Severely.
☐ Totally

**Q3. How much are you troubled with lack of confidence in your knee?**
☐ Not at all.
☐ Mildly.
☐ Moderately.
☐ Severely.
☐ Totally

**Q4. In general, how much difficulty do you have with your knee?**
☐ Not at all.
☐ Mildly.
☐ Moderately.
☐ Severely.
☐ Totally

## v Lysholm score **(Briggs et al., 2009)**

Used also to evaluate knee functions, composed of 8 main items (limp, support, locking, instability, pain, swelling, stairs-climbing, squatting).

**SECTION 1 - LIMP**

- I have no limp when I walk. (5)
- I have a slight or periodical limp when I walk. (3)
- I have a severe and constant limp when I walk. (0)

**SECTION 2 - Using cane or crutches**

- I do not use a cane or crutches. (5)
- I use a cane or crutches with some weight bearing. (2)
- Putting weight on my hurt leg is impossible. (0)

**SECTION 3 - Locking sensation in the knee**

- I have no locking and no catching sensation in my knee. (15)
- I have catching sensation but no locking sensation in my knee. (10)
- My knee locks occasionally. (6)
- My knee locks frequently. (2)
- My knee feels locked at this moment. (0)

**SECTION 4 - Giving way sensation from the knee**

- My knee gives way. (25)
- My knee rarely gives way, only during athletics or vigorous activity. (20)
- My knee frequently gives way during athletics or other vigorous activities. In turn, I am unable to participate in these activities. (15)
- My knee frequently gives way during daily activities. (10)
- My knee often gives way during daily activities. (5)
- My knee gives way in every step I take. (0)

**SECTION 5 – PAIN**

- I have no pain in my knee. (25)
- I have intermittent or slight pain in my knee during vigorous activities. (20)
- I have marked pain in my knee during vigorous activities. (15)
- I have marked pain in my knee during or after walking more than 1 mile. (10)
- I have marked pain in my knee during or after walking less than 1 mile. (5)
- I have constant pain in my knee. (0)

**SECTION 6 – SWELLING**

- I have swelling in my knee. (10)
- I have swelling in my knee on 1y after vigorous activities. (6)
- I have swelling in my knee after ordinary activities. (2)

- I have swelling constantly in my knee. (0)

**SECTION 7 – CLIMBING STAIRS**

- I have no problems with climbing stairs. (10)
- I have slight problems with climbing stairs. (6)
- I can climb stairs only one at a time. (2)
- Climbing stairs is impossible for me. (0)

**SECTION 8 – SQUATTING**

- I have no problems squatting. (5)
- I have slight problems squatting. (4)
- I cannot squat beyond 90 degrees bend in my knee. (1)
- Squatting is impossible because of my knee. (0)

**Total points from 0 to 100, the best score is 100 and means no problem in the knee and the worst score is zero and represents extremely disabled knee.**

# Radiological score used in the assessment (MOCART score- Magnetic Resonance Observation of Cartilage repair Tissue)

All patients were radiologically examined before surgery and at the time of follow up when indicated. Preoperatively, an MRI examination and a conventional x-ray examination of the knee joint in anteroposterior, lateral as well as axial views were done. A long leg x-ray was also done to measure the mechanical axis and to address the alignment of the knee joint. Postoperatively MRI was done for all patients, only x-rays were performed if indicated and if a bony procedure was done for example as in corrective osteotomy.

**MOCART score (Magnetic Resonance Observation of Cartilage Repair Tissue) (Choi et al., 2008)**

The MRI is a non-invasive method of evaluation of patients and it allows an appropriate evaluation and follow-up of the cartilage tissues as well as repair. It allows also very good evaluation of the soft tissues, articular cartilage and also the repair tissue. **(Marlovits et al., 2004; Schibany et al., 2005)**

Many recent publications, showed a successful application of the MOCART score in the follow-up of different cartilage procedures. **(Henderson et al., 2006)**

The evaluation is performed on axial, coronal and sagittal (2D) planes using high spatial resolution with slice thickness of 2-4mm.

Postoperative imaging is recommended as a useful method to assess the cartilage healing, as well as to identify any complication that may arise.

In our study, we used the MRI as a less invasive follow-up tool that allows a comprehensive assessment of the repair tissue, cartilage-bone interface. **(Glaser et al., 2005; Link et al., 2007; Marlovits et al., 2006; Takahashi et al., 2006)**

The minimum requirement to assess the cartilage with MRI is with 1.5 Tesla. The evaluation with 3.5 -Tesla MRI is better as it can produce higher quality and resolution images. Some investigators reported that the use of MR arthrography in the assessment of MACT help in differentiation between delamination of the graft base and the normal high-intensity repair tissue in the immediate postoperative period. **(Boden et al., 1997)**

The patients in this study were examined with 3,5 Tesla MRI device in the radiology institute of the University hospital of the Technical university in Munich, Germany (Klinikum rechts der Isar)

For ethical reasons, a biopsy from the implants in the postoperative period was not done and not accepted. The healing process of the implants in vivo was only assessed and controlled by means of MRI.

MOCART scoring system that is used for the evaluation of the result of treatment with autologous chondrocyte transplantation

Table 6 Parameters of the MOCART score

| Parameter | Points |
|---|---|
| **1. Degree of defect repair and filling** | |
| • Complete (at the level of the adjacent cartilage). | **20** |
| • Hypertrophy (over the level of the adjacent cartilage) | **15** |
| • Incomplete (under the level of the adjacent cartilage): | |
| ○ > 50% of the adjacent cartilage | **10** |
| ○ <50% of the adjacent cartilage | **5** |
| • Subchondral bones are freed (complete detachment or dislocation). | **0** |
| **2. Integration with border area** | |
| • Complete (complete integration in the adjacent cartilage) | **15** |
| • Incomplete (incomplete integration in the adjacent cartilage) demarcation visibly limited (split-like) | **10** |
| • Cartilage defect visible: | |
| ○ <50% of the length of the repair tissue | **5** |
| ○ > 50% of the length of the repair tissue | **0** |
| **3. Quality of repair tissue surface:** | |
| • Surface is intact | **10** |
| • Surface is damaged (fibrillations, fissures): | |
| ○ <50% of the depth of the repair tissue | **5** |
| ○ > 50% of the depth of the repair tissue | **0** |
| **4. Structure of repair tissue** | |
| • Homogeneous | **5** |
| • Inhomogeneous or cleft formation | **0** |
| **5. Signal characteristics of repair tissue** | |
| **Dual T2- FSE:** Isointense | **15** |
| Moderate intensity | **5** |
| Strong intensity | **0** |
| **3D-GE-FSE:** Isointense | **15** |
| Moderate intensity | **5** |
| Strong intensity | **0** |
| **6. Status of subchondral Lamina** | |
| • Intact | **5** |
| • Not intact | **0** |
| **7. Integrity of subchondral bone** | |
| • Intact | **5** |
| • Not intact (bone marrow edema, granulation tissue, cysts) | **0** |

| | |
|---|---|
| **8. Presence of adhesions** | |
| • no | **5** |
| • yes | **0** |
| **9. Presence of Knee effusion** | |
| • no | **5** |
| • yes | **0** |
| | |
| **Maximum score** | **100** |

After cartilage repair operations, the ideal repair tissue should have the same thickness as the adjacent native cartilage tissue, the margins of the repair tissue, should be continuous with the surrounding native articular cartilage (smooth articular surface). **(Alparslan et al., 2001; Marlovits et al., 2004)**

"The ability of MRI to describe the subchondral bone and bone marrow gives it an advantage over arthroscopy. However, the true dimensions of a cartilage defect might be underestimated at MR imaging, if the defect is not imaged in all three planes or if the intersection gap is too large". **(Glaser et al., 2007)**

ICRS (International Cartilage Research Society) recommended the following MRI sequences for the best evaluation of cartilage repair:

**a) Intermediate- weighted fast SE:**
- with fat saturation
- without fat saturation

**b) T2- weighted fast SE:**
- with fat suppression
- without fat suppression

**c) T1- weighted GRE**
- with chemical fat suppression
- with water excitation (this sequence is not available on all MR imaging systems but, if available, can be substituted for chemical fat suppression, which require acquisition time.

The evaluation of cartilage repair tissues can be done with the same method as in native cartilage as recommended by ICRS.

**Parameters of MRI evaluation of ACI/ MACT:**
**(Choi et al., 2008)**

**ACI/ MACT:**

- Degree of filling of defect by transplanted osteochondral plugs.
- Restoration of radial curvature of joint surfaces.
- Presence or absence of displacement of the graft.
- Peripheral integration of repair cartilage and osseous components.
- Morphologic characteristics of the repair site.
- Integrity of host cartilage.

The use of MRI to evaluate the patients postoperatively is correlated with the clinical examination and scores value. The parameters that are assessed with MRI at areas of autologous grafts are shown above and they include the degree of defect filling, the presence or absence of subchondral bone formation, the extent of integration of repair tissue with adjacent tissues (extension of repair tissue beyond the adjacent subchondral plate to include new bone formation), the characteristics of the graft substance and surface, and the appearance of the underlying bone.

# 5 Results

In the period from 2009 to 2014, 15 patients with multiple cartilage lesions in the knee joint were treated with multiple (MACT) in the knee joint at the sport's orthopedic department at the Technical University hospital in Munich. The average mean time between the beginning of symptoms and the operation was 37.5 Months. The symptoms started acutely in 5 patients while started gradually in 10 patients.

## 5.1 Patients collection

The patient group included 10 (66.66%) males and 5 (33.33%) females. The mean age of patients at the time of matrix implantation was 32.6 years (SD 8.67). The range of patients' age was between 19 and 45 years. The mean weight of the patients at the time of operation was 78.13 kg (SD 10.30) with a mean body length of 177 cm (SD 8.59). Thus, the average body mass index was 24.93 (SD 2.27).

The size of single cartilage defect varied between 2.5 and 6.25 $cm^2$, as every patient has 2 lesions; the average size of the defects per patient ranged from 3.75$cm^2$ to 10.5 $cm^2$. The mean size of the cartilage defects was on average 7.25 $cm^2$ (SD 2.42). A total of 30 treated cartilage defects were included in the study. All the treated lesions are grade III or IV according to Outerbridge classification.

Table 7 Criteria of the patients

| **Criteria** | |
|---|---|
| Gender | 10 males (66,66%), 5 females (33,33%) |
| Age at time of the operation | 32.6 (19-45) years old |
| Weight | 78.13 (60-93) kg |
| Length | 177cm (154-188) |
| BMI | 24.93 (21.5-29.4) |
| Site of the lesions (30 lesions in 15 patient) | • Medial femoral condyle (MFC) + Trochlea (n=4 patients)<br>• Medial femoral condyle (MFC) + Patella (n=1 patient)<br>• Lateral femoral condyle (LFC) + Patella (n=1 patient)<br>• Patella (n= 4 patients)<br>• Trochlea (n=1 patient)<br>• Patella + Trochlea (n=4 patients) |
| Size of the defect | (2.5 $cm^2$- 6.25$cm^2$)<br>**per patient** = 7.25$cm^2$ (3.75$cm^2$-10.5$cm^2$) |
| Etiology and number of patients | • traumatic: n=7<br>• non- traumatic: n=6<br>• OCD: n=2 |
| Beginning of the symptoms | gradual (n= 10), acute (n= 5) |

| | |
|---|---|
| Operations that took place before MACT | • Microfracture, cartilage smoothing/ debridement, lateral release of the patella and removal of foreign body: (n= 1)<br>• Lateral release, tibial tuberosity transfer, screw removal after tibial tuberosity transfer: (n= 1)<br>• chondroplasty, arthrolysis: (n= 2)<br>• Osteochondritis dissecans fixation: (n= 1)<br>• HTO (high tibial osteotomy), medial meniscus ganglion removal, chondroplasty: (n= 1)<br>• Pridie drilling, OATS: (n= 1)<br>• MACT contralateral knee: (n= 1)<br>• Femur shaft fracture fixation+ 2 times inferior patella resection due to patellar tip syndrome (Jumper's knee): (n= 1)<br>• no previous operations: (n= 6) |
| Operations done with the first step of MACT (during harvesting of cartilage samples)<br><br>Operations done with 2nd step of MACT (with membrane fixation) | • Lateral release: (n= 1)<br>• Spongioplasty: (n= 1)<br>• HTO revision (because of over-correction during the first operation): (n= 1)<br>• Lateral meniscus partial resection: (n= 1)<br>• Medialization of Tibial tuberosity, patella denervation und facetectomy: (n= 1)<br>• MPFL (medial patellofemoral ligament reconstruction): (n= 1)<br><br>• Open wedge HTO: (n= 1) |
| Operations done after MACT | • ORIF (open reduction and internal fixation) of distal femur after supracondylar femur fracture, Re-ORIF + axis correction and spongioplasty after pseudoarthritis, Re-Re- ORIF after plate loosening, plate removal: (n= 1) |
| Smoking | 5 Smokers, 10 non-smokers |
| Complications | • Repeating the arthroscopic harvesting of the cartilage biopsy due to non-viability of the cartilage cells on the membrane after thawing, harvesting of the cartilage samples was repeated: (n= 1)<br>• pain persistence: (n= 2)<br>• patellofemoral arthritis: (n= 1)<br>• non-painful patellofemoral crepitation: (n= 11) |

## 5.2 General assessment

At the postoperative follow-up, in the period between October 2014 and March 2016, the patients were questioned about the overall assessment of the procedure. It was found that the patients were generally satisfied after the surgical procedure.
13 (86.66%) of the 15 questioned patients responded to the question of the overall assessment with "satisfied" or "very satisfied". From these 13 patients, 2 of them said they were "very satisfied", 2 patients (13.33%) “were not satisfied" due to persistent pain, complications or over expectations. **Fig. 17**


Figure 17 Satisfaction of the patients

## 5.3 VAS

Comparing with preoperative data regarding the intensity of pain, it is found that the pain is significantly reduced at the time of follow-up. Preoperatively, the patients had mean VAS of 6.86 (SD 1.68). The improvement of pain intensity at the time of the follow up is compared with the preoperative values and it is found to be significantly reduced to 1.28 (SD 1.56) at the time of follow-up.

A significant relation ($p < 0.001$) was found between cause of the lesion and the intensity of pain reduction at the time of the follow-up. The patients who suffered from cartilage lesions as a consequence of traumatic incidents have the best results with regard to pain intensity reduction at the time of follow-up. **Fig. 18**

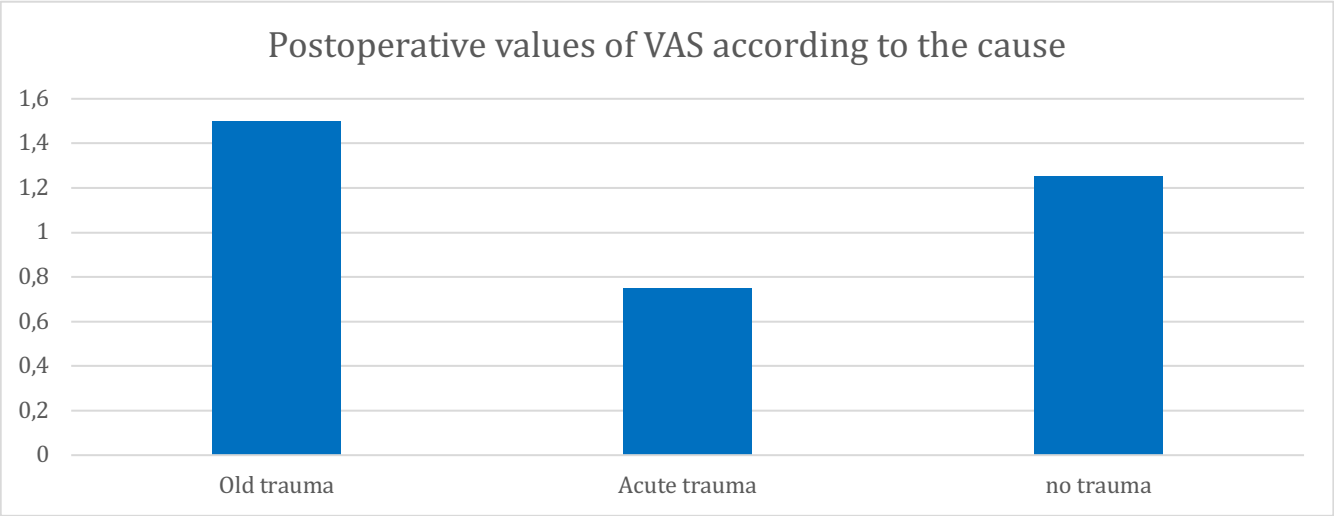



Figure 18 Values of VAS at the time of follow-up according to the cause of the lesion

## 5.4 IKDC score

The mean preoperative IKDC score was 47.88% and postoperatively at the time follow up was 79.80% with significant improvement about 31.92%. **Fig. 19**

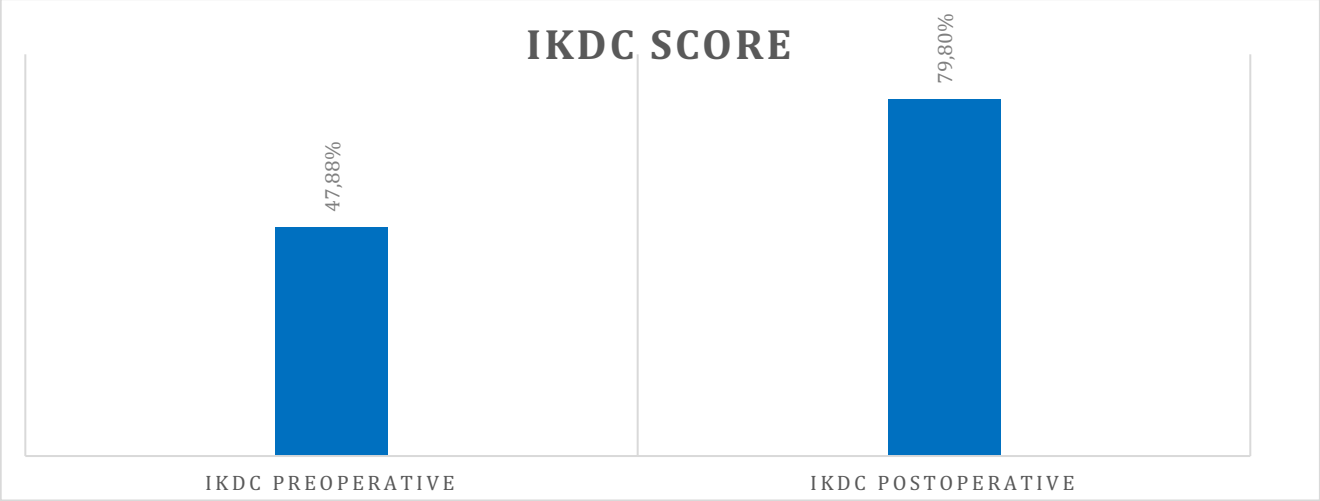



Figure 19 preoperative and postoperative IKDC score

In one patient, the IKDC score result should be considered separately due to a specific postoperative course. After MACT operation this patient suffered from distal femur fracture, after motorcycle accident, and he was treated with open reduction and internal fixation with plate and screws, postoperatively he suffered from popliteal vein injury and thrombosis, which required surgical intervention by the vascular surgeons. In the course of follow-up, he acquired postoperative infection and non-union of the treated fracture. The patient has then undergone multiple operations after that to get rid of the infection and to get a re-stabilization of the infected

non-united broken femur with a new plate and screws osteosynthesis, these were removed after union of the fracture. In the follow-up assessment, a clear deterioration of the IKDC result was seen in his case in comparison with the time before the MACT operation. This case must be considered when interpreting the results.

It was shown that the patient who suffered from acute trauma had the best IKDC score (89.60%), while patients who had an old trauma scored 64.38% and the least score was found in patients who had no traumatic incidents 55.10%. **Fig 20**

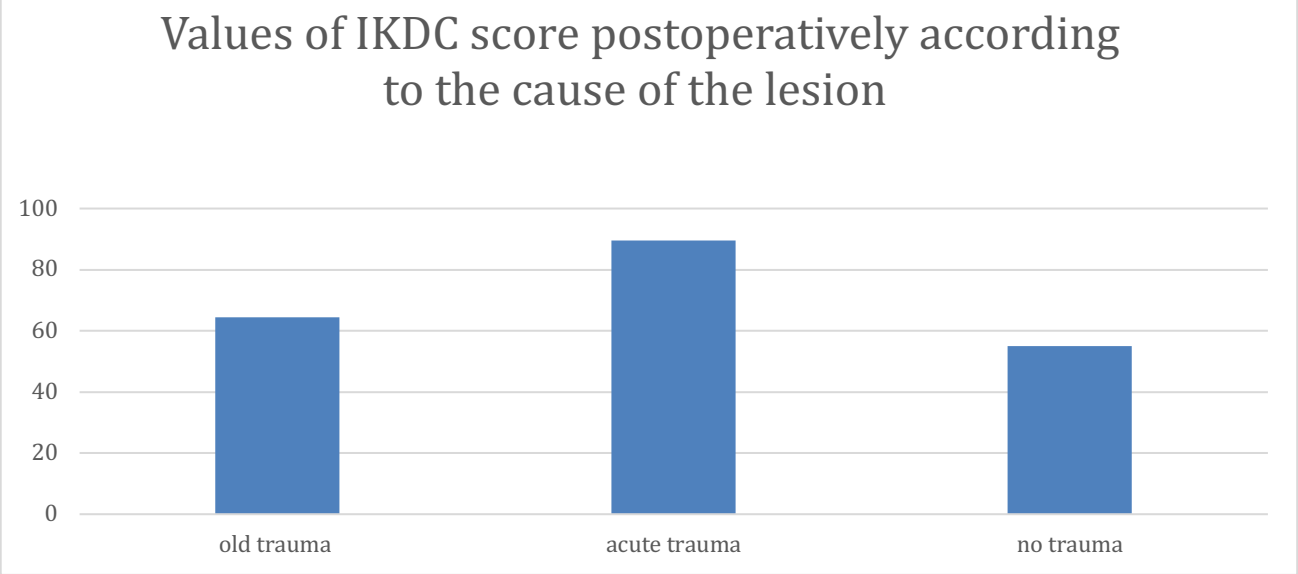



Figure 20 values of IKDC score postoperatively according to the cause of the lesion

## 5.5 Tegner activity scale

All the examined patients mentioned an improvement in the Tegner activity scale at the time of the follow-up in comparison to the preoperative time, the mean postoperative value is 5 (SD 2.0), the mean preoperative value was 2.0. This is statiscal good, as this means that there is positive alteration between pre and postoperative values. There is no significant influence (p-value is 0.93 with Spearman Rank-Order correlation). **Fig. 21**

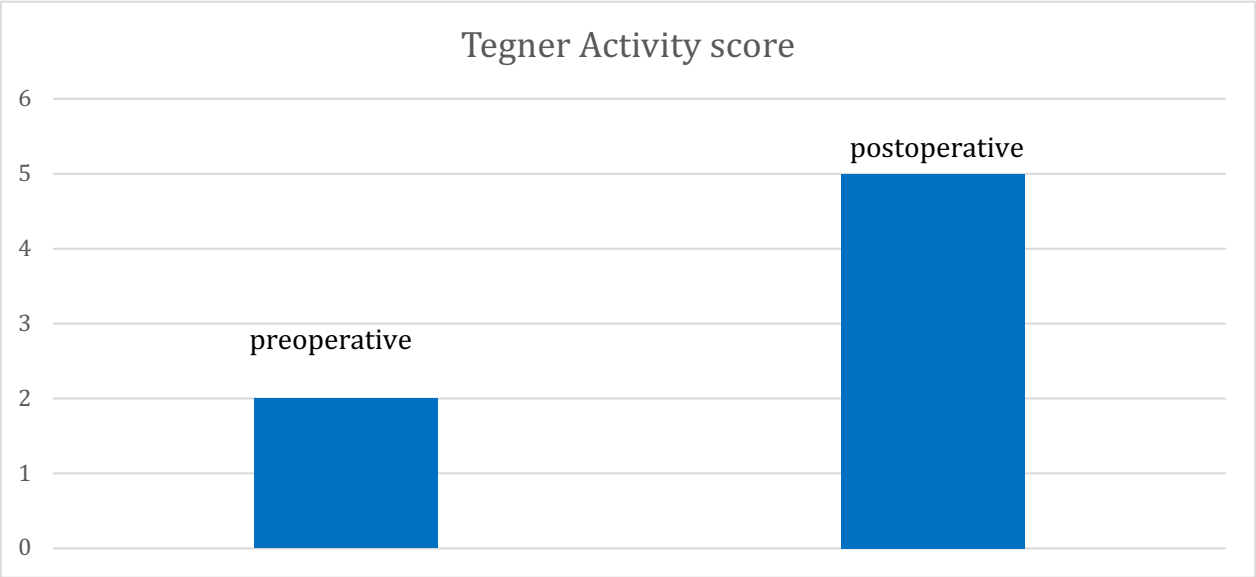



Figure 21 Tegner activity scale pre- and postoperative

## 5.6 Knee injury and Osteoarthritis Outcome Score (KOOS)

The multilocular MACT has a positive impact on the KOOS, the mean preoperative score is improved from 37.38 to 70.78 (SD 18.50) postoperatively for the 5 subscales was with improvement of about 33.4, the score ranges postoperatively from 38.1 as the worst score and 95.2 as the best score.

This is statiscal good, as this means there is positive alteration between pre and postoperative values. There is no significant influence (p-value is 0.76 with Spearman Rank-Order correlation). **Fig. 22**

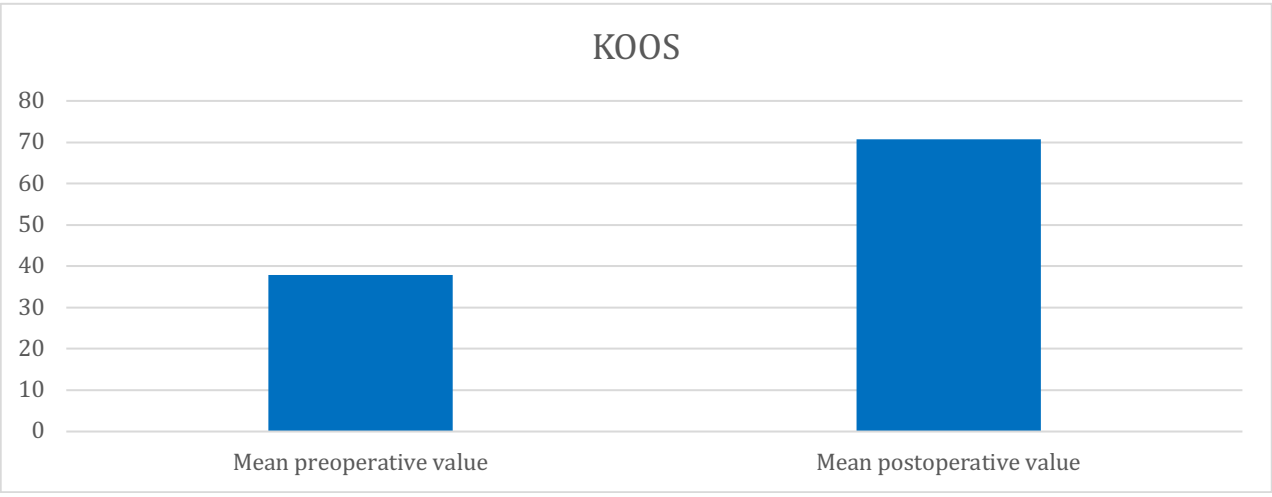



Figure 22 Knee injury and osteoarthritis outcome score

## 5.7 Lysholm score

In our study, there was an improvement of the Lysholm score in 13 patients out of 15 patients. 1 Patient had the same score and one patient had lower score in comparison with the preoperative value. The preoperative mean Lysholm score was 66.42 (SD 8.52), while the mean postoperative value was 79.28 (SD 18.13). This is statiscal good, as this means there is positive alteration between pre and postoperative values. There is no significant influence (p-value is 0.44 with Spearman Rank-Order correlation). **Fig. 23**

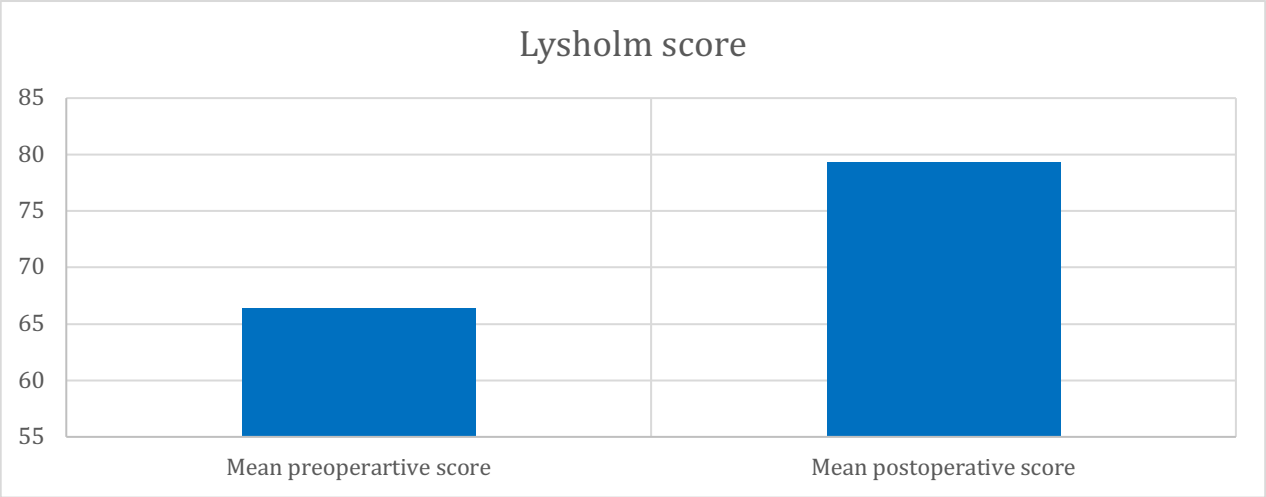



Figure 23 Lysholm score

## 5.8 MOCART score results

Each of the examined patients has 2 lesions at the knee joint, with a total of 30 lesions in different compartments of the knee. The average results were 73.125 points (SD 16.90) at the time of the follow-up. The higher score was 100 points and the lower was 35.

In the examination of the individual findings, a complete filling of the cartilage defect was seen in 18 of the 30 the cartilage defects (60%). In 1 patient only, one cartilage defect was slightly hypertrophied (3.33%). In 4 lesions (13.33%) the cartilage defect was only <50% filled, while in 7 lesions >50% of the defect was filled (23.33%). None of the lesions showed exposed subchondral bones.

The integration of the implant into the surrounding cartilage was also predominantly complete in (66.66%, n = 20). In 6 of the examined cartilage defects (20%) the boundary between the implant and articular cartilage was visible ("split-like"). The remaining 4 cartilage defects were only partially filled (13.33%).

The assessment of the implants revealed an intact and homogenous surface in 16 lesions (53.33%) as well as a predominantly homogeneous structure of the implant (26.66%, n = 8).

20% (n = 6) showed an inhomogeneous structure. A high degree of destruction of the implant ("cleft formation") was not be observed in any lesion.

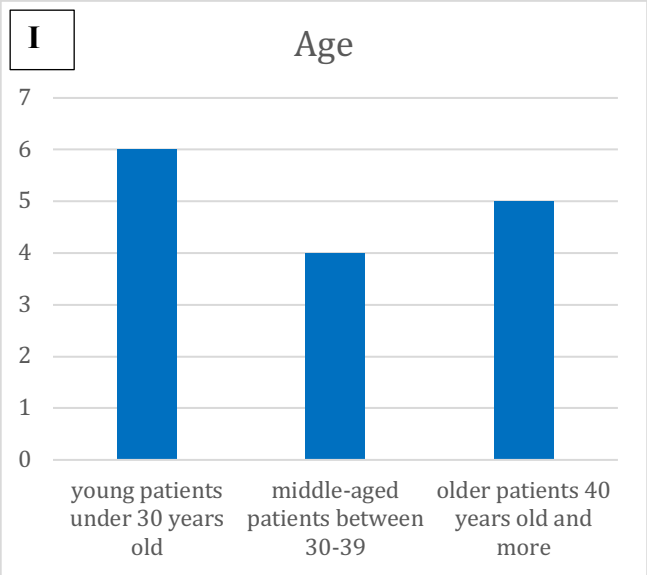
The signal intensity of lesions in Dual T2-FSE was in the majority of the transplanted membranes isointense (60%, n= 18), moderately hyperintense in 12 cases (40%) while none of the cases showed marked hypointense signal. The subchondral lamina was intact in 24 lesions (80%), while was no longer intact in 6 lesions (20%). Slight adhesions were found in MRI in 4 patients (3 of them followed an old trauma while only 1 after OCD).

In 46.66% of the implants (n = 14) subchondral edema was observed, while there was no subchondral edema in 16 lesions (53.33%). However, no clear causes or clinical correlation could be established.

## 5.9 Results of the individual criteria

### i Age:

The patients included in this study had a mean age of 32.6 years (SD 8.67) at the time of the MACT, age ranged from 16 to 46 years old. The patients in this study were divided into the following groups: young patients under 30 years (40%, n = 6) and middle-aged between 30-39 (26.66%, n=4) and older patients 40 years (33.33%, n = 5). It was found that here is no significant influence of age of the patients on IKDC score. (p-value 0.29 using Chi-square test). **Fig 24**



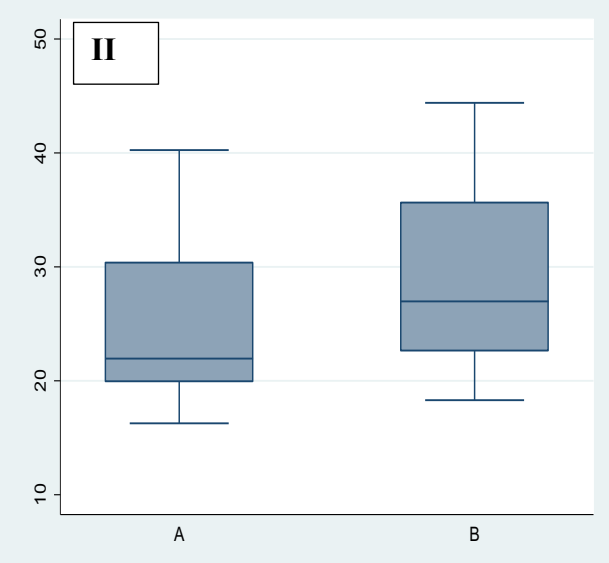




Figure 24 (I) Age groups (II) Influence on IKDC score (A= IKDC A, B= IKDC B)

Also, there was no correlation was found between the age of the patients on the operation day and the MOCART score at the follow-up day (p-value 0.31 using the Spearman Rank-Order correlation)

## ii Gender

Gender versus IKDC score

A total of 10 males (66,6%) and 5 females (33.3%) were treated with multiple MACT. Both men and women achieved significantly better results in the IKDC score at the time of the follow-up compared to the preoperative condition.

In the male group, there was a mean improvement in the IKDC about 48% at the time of follow-up, while in the female group the mean improvement was 32%. No significant influence of gender on IKDC score (p-value 0.85 using Chi-square test). **Fig. 25**

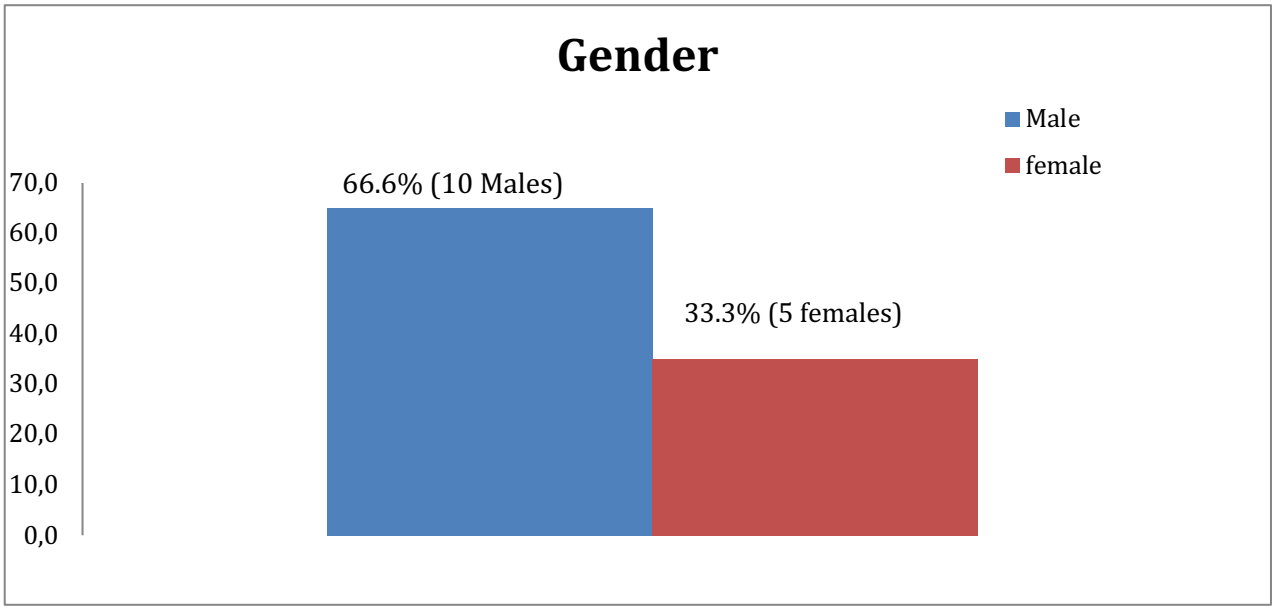



Figure 25 Gender distribution versus IKDC

Gender versus MOCART score

Gender of the patient showed significant influence on MOCART score. It was found that the female patients have lower MOCART score (p-value using Mann Whitney U-Test). **Fig. 26**

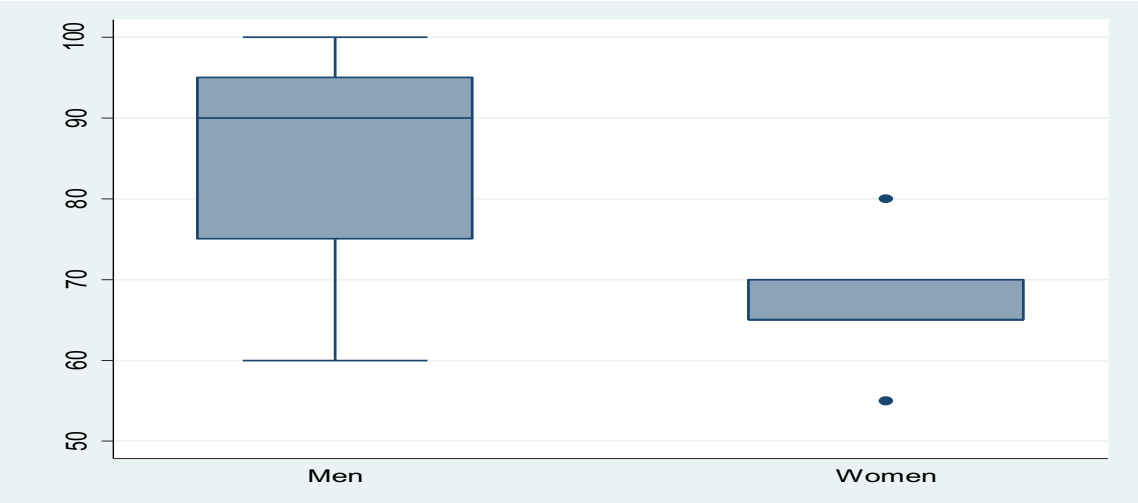



Figure 26 Gender versus MOCART score

## iii Body-Mass-Index (BMI)

9 patients (60%) had normal BMI (19-23) at the time of surgical procedure, while 6 patients (40%) were overweight (BMI 26-29). The mean body weight of our patients at the time of operation was 78.13 kilogram (SD 10.30) with a mean body height of 177 centimeter (SD 8.59). The body mass index showed a value of 24.93 (SD 2.27). **Fig. 27**

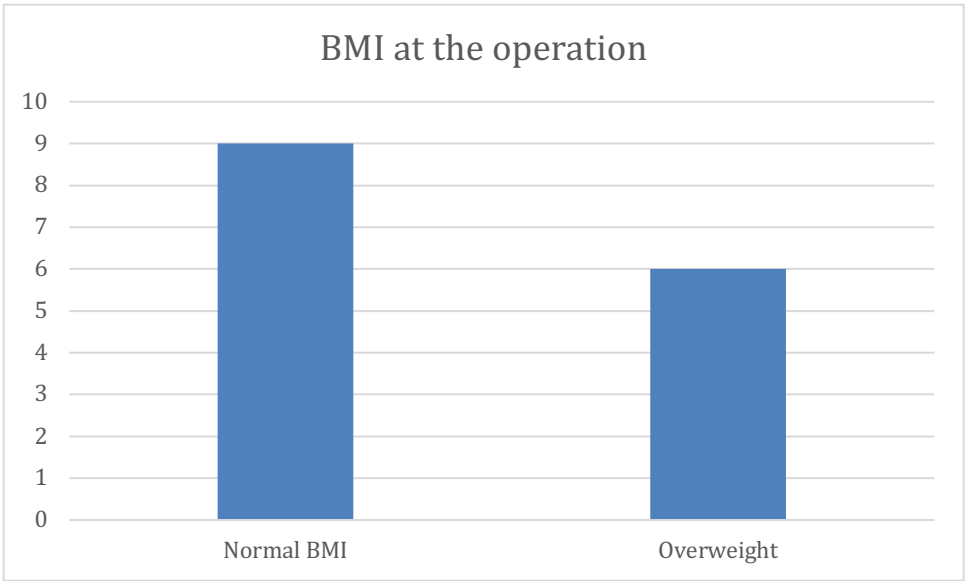



Figure 27 BMI at operation time

## BMI versus IKDC

In the correlation of the body mass index with the IKDC result, it was found that the patients who had less BMI at the time of the operation had better IKDC score. (p-value 0.58 using Mean-Whitney U Test). **Fig. 28**

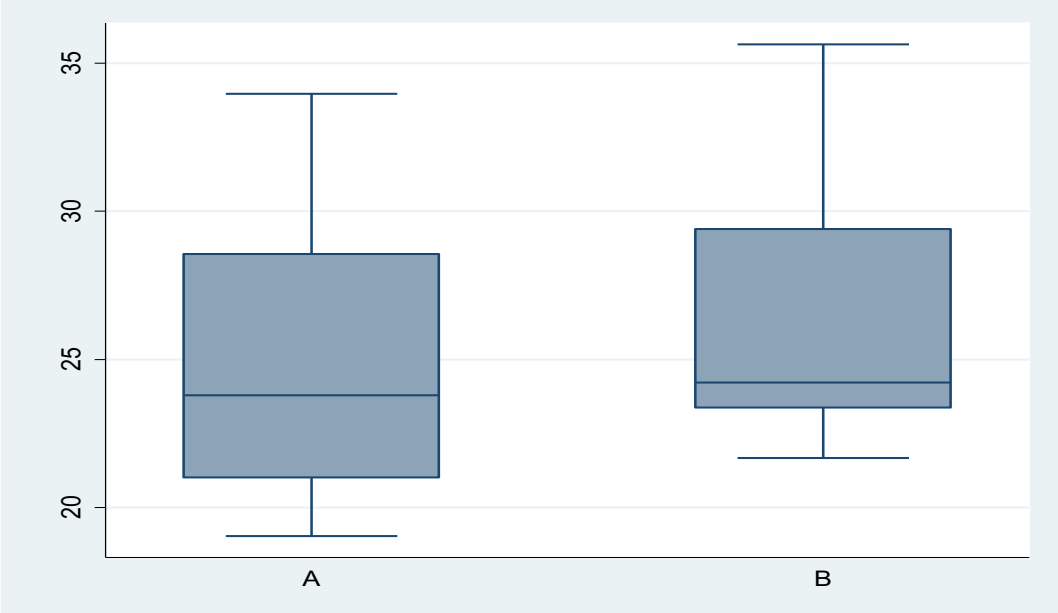



Figure 28 BMI versus IKDC score (A= IKDC A, B= IKDC B)

## BMI versus MOCART score

A significant inverse correlation was found between the body mass index and the MOCART score (p-value < 0.001 using Spearman Tank-Order correlation). **Fig. 29**

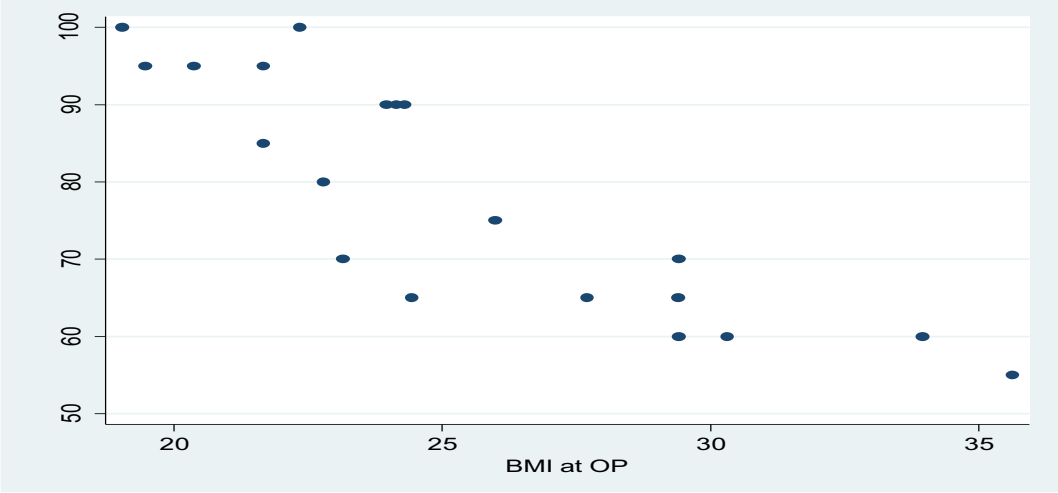



Figure 29 BMI vs MOCART score

## iv Etiology of the lesion

The causes of cartilage defects in our patients were diverse. In this study, a distinction was made between non-traumatic (n=6, 40%), traumatic incidences (n= 7, 46.66%) and OCD (n= 2, 13,33%). **Fig. 30**

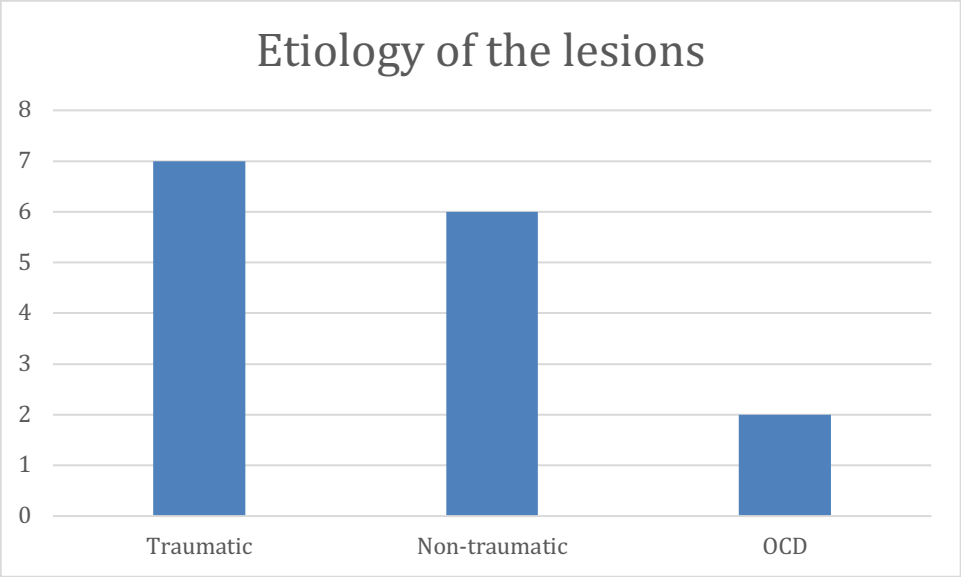



Figure 30 Etiology of the lesions

## Etiology vs IKDC:

In clinical follow-up, the patients with acute trauma or OCD had an excellent outcome with regard to IKDC score (89.6%). On the other hand, the patients who reported a traumatic event that was longer than 12 months showed lower mean IKDC results at the time of the follow up (mean value was 64.38%), in the non-traumatic lesions the results were at lower level (mean value was 55.1%).

There is no significant influence of etiology of the lesion on the IKDC score (p-value 0.33 using Chi-square).

Table 8 Etiology versus IKDC

| **Etiology** | **IKDC A** | **IKDC B** | **Total** |
|---|---|---|---|
| **Traumatic** | 5 | 2 | 7 |
| **Non-traumatic** | 2 | 4 | 6 |
| **OCD** | 2 | 0 | 2 |
| **Total** | 9 | 6 | 15 |

## Etiology versus MOCART score:

Etiology of the lesion is not correlated with MOCART score (p-value 0.32 using Mann- Whitney U test). **Fig. 31**

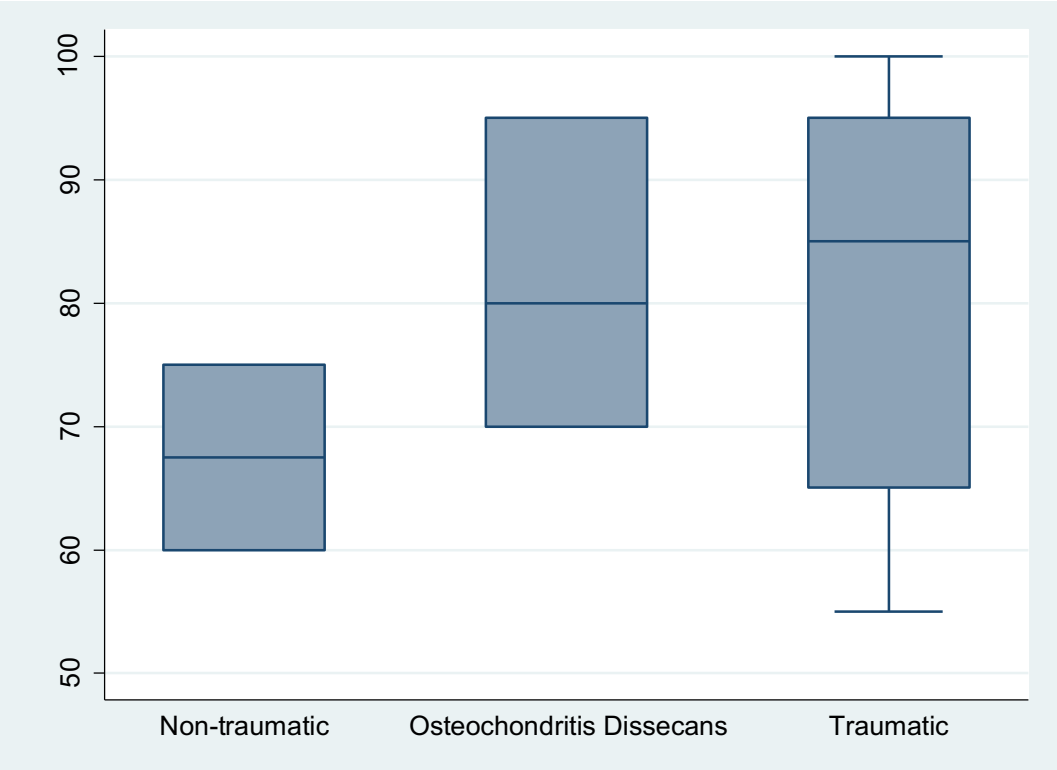



Figure 31 Etiology vs MOCART Score

## v Site of the lesion

A clear improvement of the results in the IKDC score was shown at the time of the follow-up in the different localities of the lesions.

Table 9 Relationship between defect localization and IKDC

| **Defect localization** | **No. of patients** | **IKDC preoperative** | **IKDC at time of follow up** | **Improvement** |
|---|---|---|---|---|
| **Patella+ trochlea** | 4 | 44.6 | 69.5 | 24.9 |
| **Patella** | 4 | 36.2 | 72.6 | 36.4 |
| **MFC+ trochlea** | 4 | 52.9 | 82.4 | 29.5 |
| **MFC+ patella** | 1 | 49.3 | 84.2 | 34.9 |
| **Trochlea** | 1 | 48.4 | 89.6 | 41.2 |
| **LFC+ patella** | 1 | 51.9 | 81.6 | 29.7 |

The localization of the lesion has no significant influence on the IKDC score (p- value is 0.33 using Chi-square test) nor on the MOCART score (p-value 0.52 using Mann-Whitney U Test).

## vi Defect size (surface area in $cm^2$)

The cartilage defects treated in this study had an average size per patient approximately 7.25 $cm^2$ (SD 2.42). The cartilage defects per patient varied from 3.75 to10.5 $cm^2$. The patients in this study were divided into 2 groups; the first group included patients with cartilage defects with surface area less than 5 $cm^2$ (33.3%, n = 5), the second group included patients with cartilage defects larger than 5 $cm^2$ surface area (66.6%, n = 10). **Fig. 32**

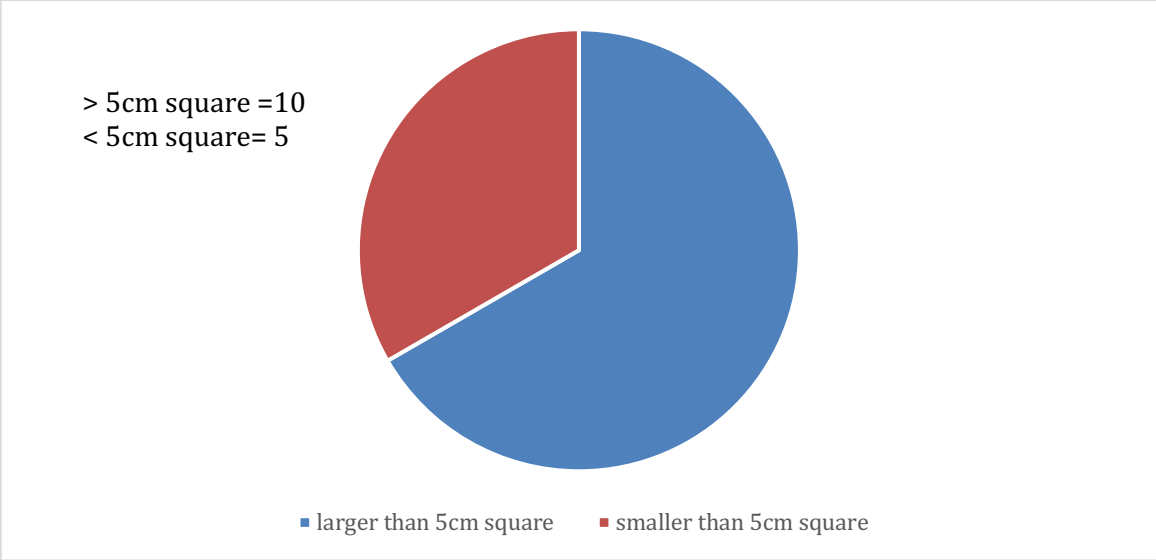



Figure 32 Distribution of the patients according to defects size

At the time of the follow-up, patients in the second group had an excellent IKDC postoperative score of 84.33%. Very good results also were observed in the first group patients but with less value of 75.30%.

However, the correlation between defect size in $cm^2$ and IKDC result at the time of the follow-up did not show a significant correlation (p-value using Mann-Whitney U test 0.78).

## Defect size vs MOCART score

No correlation was found between defect size and MOCART Score (p-value 0.66 using Spearman Rank-Order correlation). **Fig. 33**

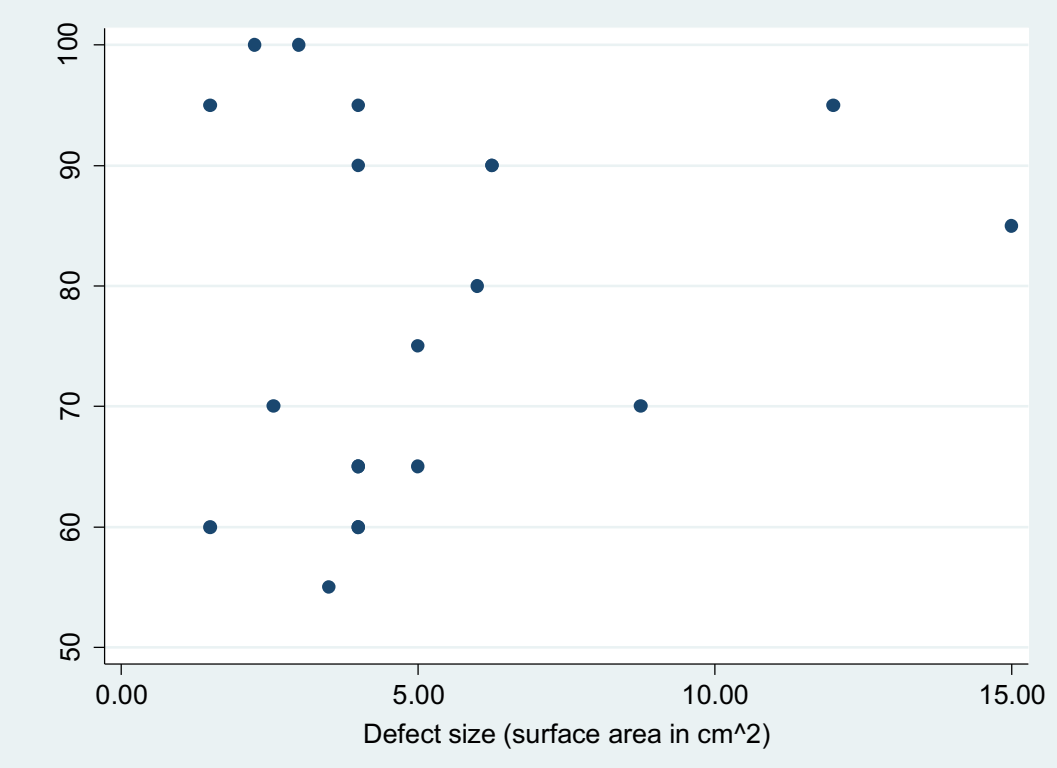



Figure 33 Defect size vs MOCART score

## vii Knee function at first examination

A distinction was made between no limitation of function (1 patient, 6.66%), limited functions (12 patients, 80%), very limited function was described in (2 patients, 13.33%). **Fig. 34**

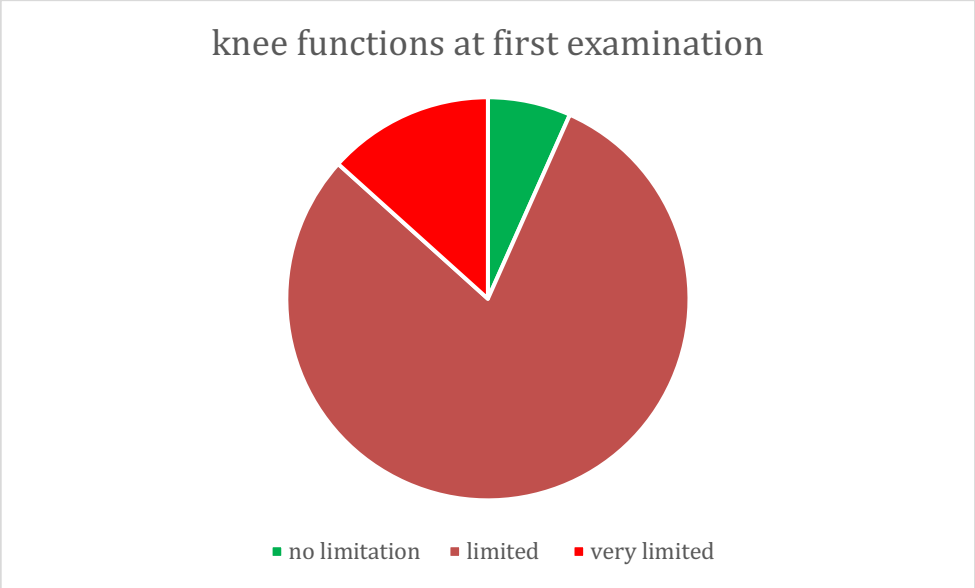



Figure 34 Knee function at first examination

## Knee function at follow-up

A distinction is made between no limitation of function (6 patients, 40%), almost no limitation (8 patients, 53.33%), limited functions (1 patient, 6,66%), no patients had described their knee functions as very limited. **Fig. 35**

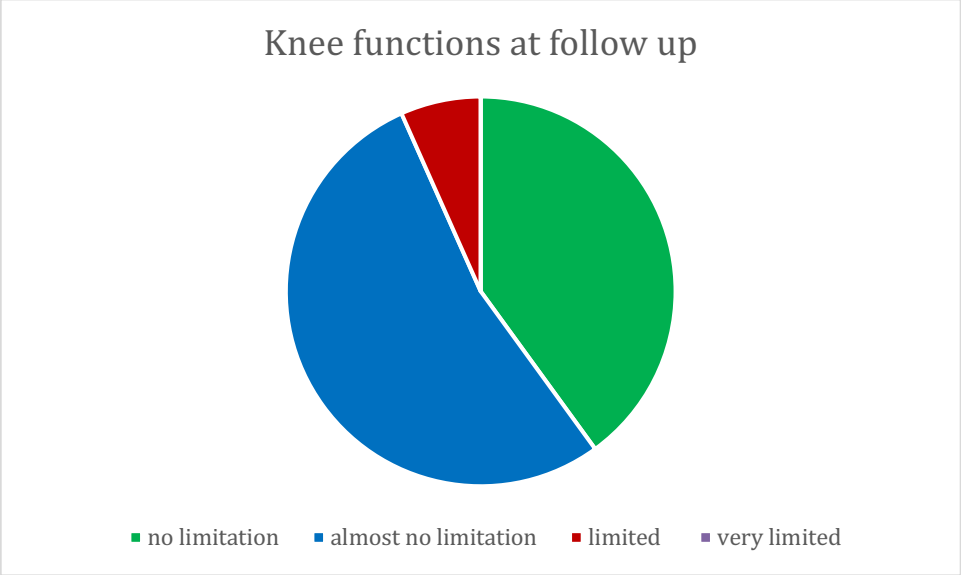



Figure 35 Knee function at follow-up

Statiscal, no correlation is found between the function status at the time of first examination and at the time of follow-up. This is found to be a good indicator, as this means there is an improvement at the time of follow-up. This is correlation is not significant (p-value 0.61 with Spearman Rank-Order correlation).

## viii Correction of leg axis

Due to varus knees, only 2 patients underwent correction of leg axis, one of them a had revision of the corrective osteotomy due to the overcorrection of the leg axis that was done before the MACT procedure. **Fig. 36**
The osteotomy performed to correct the knee varus deformity was open wedge high tibial osteotomy (HTO).

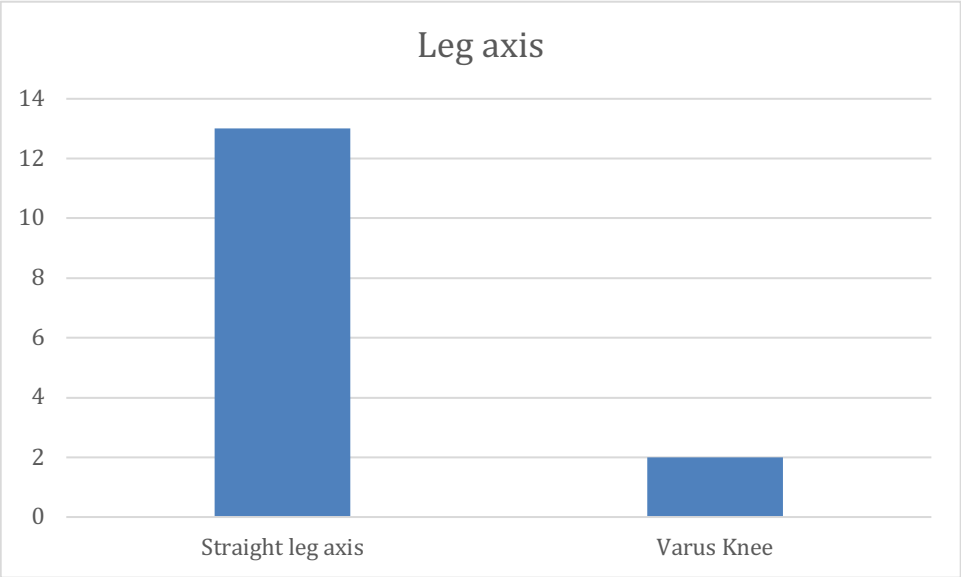



Figure 36 Leg axis

## Leg axis versus IKDC and MOCART score

Leg axis has marginal significance on IKDC (p-value 0.08 using Mann-Whitney U test), while it is not correlated with MOCART score (p-value 0.86 using Spearman Rank- Order correlation). **See fig. 37, 38**

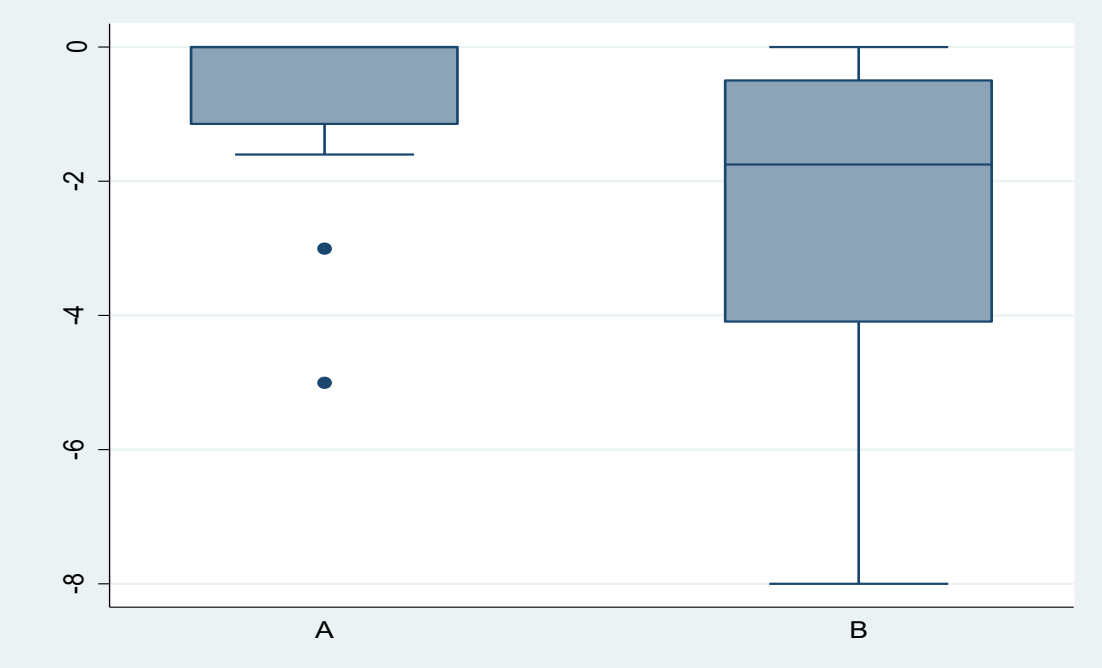



Figure 37 Leg axis vs IKDC score (A= IKDC A, B= IKDC B)

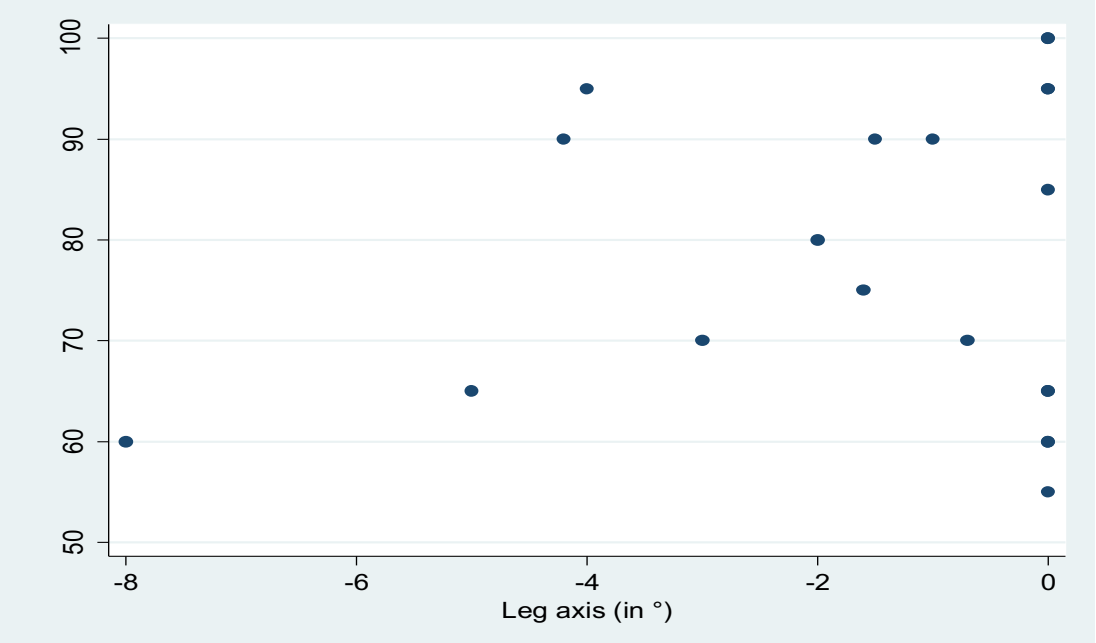



Figure 38 Leg axis vs MOCART score

## Correction of leg axis

Corrective osteotomy seems to have no significance on IKDC score (p-value 0.31 using Chi-square test), or on MOCART score (p-value 0.36 using Mann- Whitney U test). **See Fig. 39**

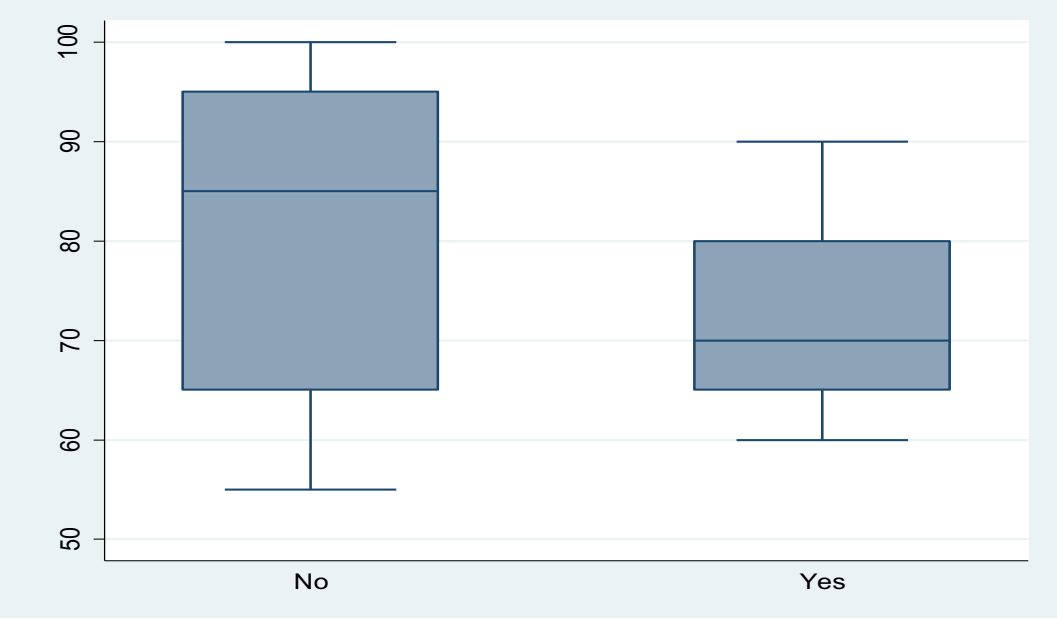



Figure 39 Correction of leg axis vs MOCART score

## ix Smoking

10 patients were non-smokers, 5 patients were smokers (1 packet/day). **See Fig 40.**
In addition, we calculated the mean numbers of cigarettes smoked by the smoker group per day, as well as the numbers of years smoked, to quantify the number of pack-years, to show the life-time exposure to smoking.

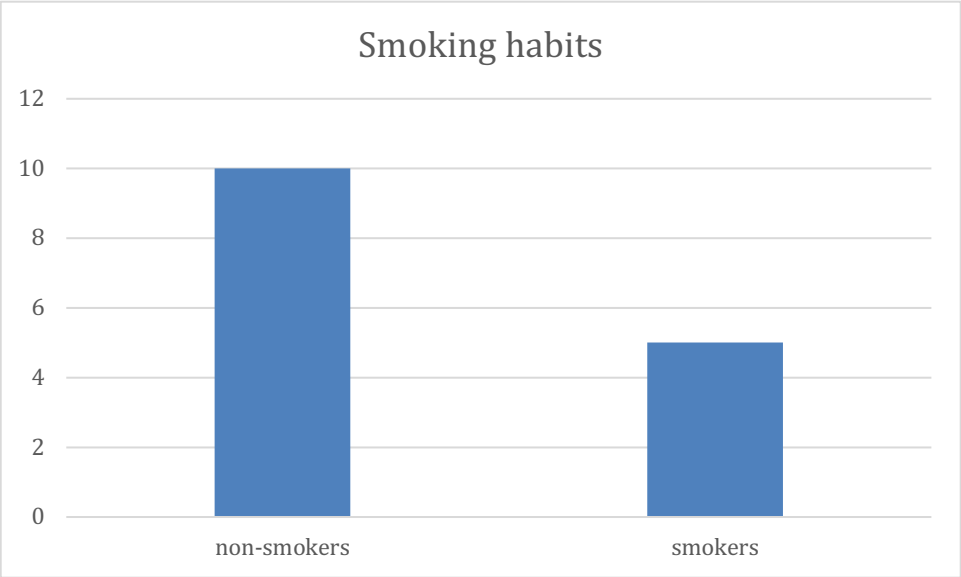



Figure 40 Smoking habits

Smoking versus IKDC score and MOCART score

No significant influence of smoking habits on both IKDC (p-value 0.64 using Chi-square test), or on MOCART score (p-value 0.38 using Mann- Whitney U test). **See fig. 41.**

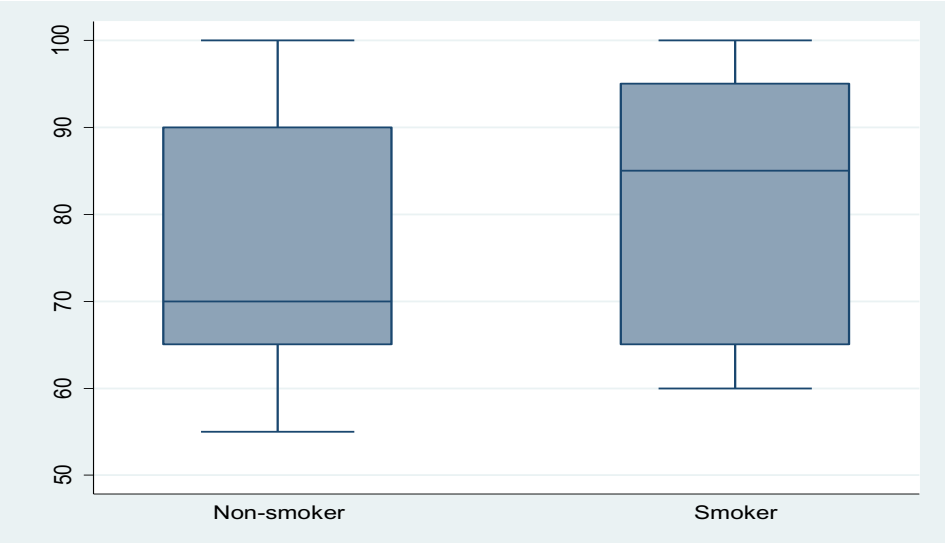



Figure 41 Smoking habits vs MOCART score

## x IKDC versus MOCART score

The IKDC score does not seem to have a significant influence on the MOCART score at preoperative and at follow-up time (p-value 0.79 using Mann- Whitney U test). **See Fig. 42**

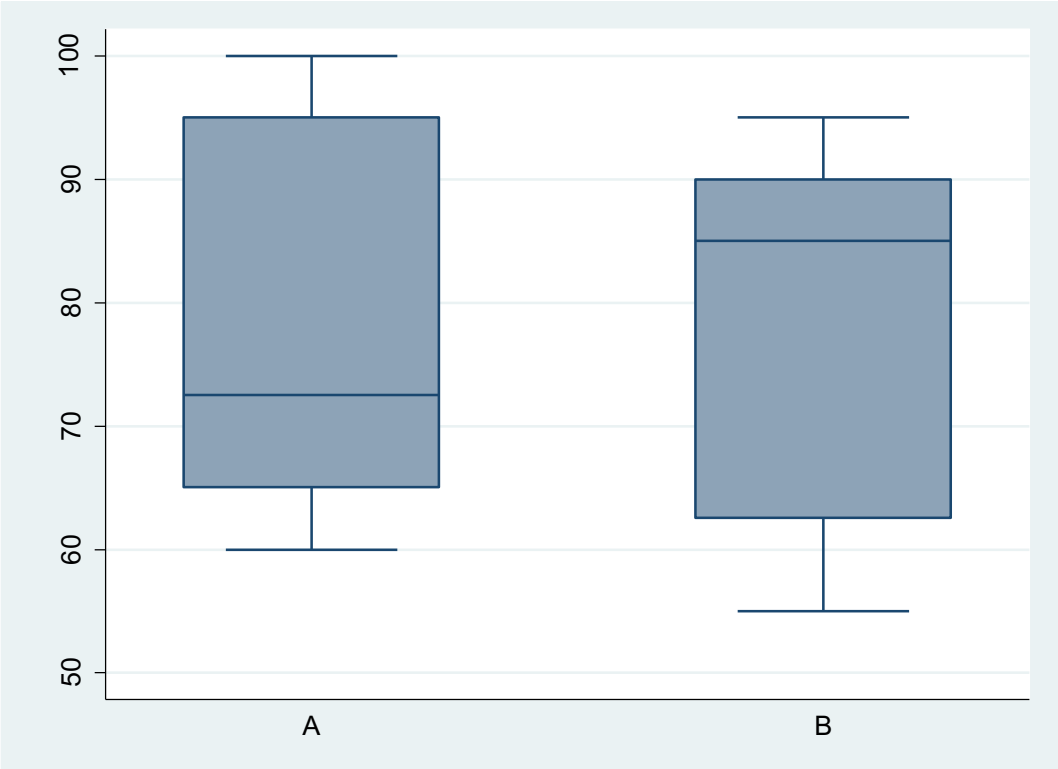



Figure 42 IKDC vs MOCART score (A= IKDC A, B= IKDC B)

### xi Additional operations

In 7 patients, additional operative measures were done with MACT; 6 patients undergone extra operations with the first step of the procedure and 1 patient undergone an operation during the second step of the procedure **(see table 7)**. The group of patients who did not undergo any co-operation had mean IKDC score 81.9% at the time of the follow-up. The patients who undergone a co-operation had IKDC score value of 77.85%.
The main goal for open wedge HTO is to shift the weight bearing from the overloaded medial side of the knee towards the opposite lateral compartment, this will lead to unload the medial compartment of the knee. **(Spahn et al., 2012)**

There was no significant difference in the IKDC values between the two groups, (p-value = 0.66). Even when comparing the time of the co-operation (first or second step), no influence on the clinical result could be shown.

## Complications:

None of our patients complained of arthrofibrosis and hence no postoperative mobilization under anesthesia or arthroscopic arthrolysis was needed, only one patient complained of non-painful limitation of flexion (120$^{o}$) and non-painful crepitation at the time of the follow-up. It should be considered that this patient suffered from a motorcycle accident after the MACT operation and had a distal femur fracture with injury of popliteal vein and DVT, postoperative infection and osteomyelitis, which has required many surgical interventions to treat his condition as debridement, plate removal and then refixation again with a new plate, which was removed after fracture healing.

This patient complained of mild pain at the time of follow up examination but fortunately, he was able to perform his daily activities and also nearly the same level of sport that he used to do before MACT operation.

One patient has undergone a repetition of harvesting the cartilage sample, as the chondrocytes were avital after thawing in the lab.

The most common complaint among our patients was the non-painful patellofemoral crepitation in those patients received MACT either in patella or trochlea. The crepitations were mainly manifested during climbing the stairs. 8 patients complained of light crepitation, 3 complained of moderate crepitation (1 patient showed hypertrophied membrane) while 4 patients had no crepitation.

One Patient showed at the time of follow-up patellofemoral arthritis and she was advised to get a patellofemoral partial replacement (the lesions were partially filled), but the patient did not want to get the operation, as she was not suffering from any pain or limitation of movements.

No single case of postoperative infection was recorded in our study after MACT operation as well as no revision or failure of the procedure was shown in our study.

# 6 Discussion

Since its clinical introduction in 1994, the autologous chondrocyte transplantation is considered an interesting focus of research for orthopedic surgeons. It droves also the attention of the media and the interest of many affected patients. **(Brittberg et al., 1994)** The possibility of providing long-term care for cartilage damage from the body's own tissue and maintaining the physiological joint function was the starting point for being the cornerstone of large number of studies. This method of operative care has a great potential. Numerous studies followed that were concerned with the optimization of this method. **(Chung & Burdick, 2008)**

In order to assess the patients after MACT, several methods were implemented to perform a comprehensive evaluation of the success of this method, this include clinical evaluation questionnaires as KOOS, Lysholm, IKDC, Tegner activity scores and VAS for pain evaluation. Furthermore, MRI represents high efficacy in the evaluation of tissue repair. Many MRI score have been reported, but the MOCART score remains the most common used scoring system for evaluation of cartilage repair tissue. **(Ebert et al., 2014)**

## 6.1 Comparison of the current study with literature

There are a lot of studies in the literature that discussed the use of the MACT in the knee joint and they introduced many comparable clinical and radiological scores. The cohort of the current study is well comparable with the patients in other studies. The current study shows various unique points:

a) The presence of multiple cartilage lesions in the knee joint and its treatment with MACT,
b) The wide variety of different examination methods (clinical scores, MRI with MOCART score). The current study has a considerable degree of novelty with regard to the presence of multiple lesions per single knee joint.

In our study, postoperatively the intensity of pain was significantly reduced. Preoperatively, patients had mean VAS of 6.86 ±1.14 and postoperatively 1.28 ± 0.97 at the time of follow-up.

The mean Lysholm score was significantly improved 79.28 from to 66.42 postoperatively. The multilocular MACT has also a positive impact on the Knee Injury and Osteoarthritic Score (KOOS), the mean value of the KOOS postoperatively in our patients was 70.78. The Tegner activity scale at the time of the follow-up is significantly improved to level 5, while the mean preoperative value was 2.0.

In a study by Ossendorf et al **(Ossendorf et al., 2011)** on 51 patients who undergone MACT for the treatment of symptomatic cartilage lesions in all knee compartments. The mean age of the patients was 36 years, the mean size of the defects was 7.25 $cm^2$. The patients were evaluated clinically by Cincinnati, Lysholm, Larson and Noyes scores. The Lysholm score was improved from 32.26 to 64.68. Their results were inferior in comparison to our results.

Ventura et al **(Ventura et al., 2012)** observed the results after MACT in 53 patients with full thickness cartilage defect of the knee joint, they followed the patients for about 24 months and MRI was done at 1 and 2 years postoperatively, at 2 years follow-up, the Lysholm score increased from 70 to 95, this result was better in comparison to our results. The VAS decreased from 5.2 to 1.9, which is comparable to our study. No significant differences in Tegner score was found, in contrary to our study, which showed significant improvement in the Tegner activity scale.

The mean preoperative IKDC score in our patients was 47.88 and postoperatively at the time follow up was 79.80 with significant improvement about 31.92. Our results were better than the results presented by Rackwitz et al. **(Rackwitz et al., 2012)**, Zak et al **(Zak et al., 2014).** In the study done by Rackwitz et al., they studied 116 patients with Outerbridge grades III-IV cartilage lesions, they evaluated the patients by IKDC score, VAS, physical and mental SF-36 score, the mean follow-up was 30.2 months, the IKDC score was improved from 42.4 to 70.5, VAS decreased from 6.7 to 3.2. Same applies to the long-term study done by Aldrian et. al. **(Aldrian et al., 2014)**, who followed 16 patients for a period of 10 years and they evaluated their patients clinically with IKDC score, KOOS, Tegner activity scale, Noyes sports activity rating scale, VAS and radiologically with MOCART score. They did not find a statistically significant improvement regarding VAS and Tegner activity scale, while IKDC score improved from 44.1 to 59.0, which was also inferior to our results.

While the results observed by Filardo et al. **(Filardo et al.,2014),** Kon et al. **(Kon et al., 2016)** and Marlovits et al. **(Marlovits et al., 2012)** were comparable to our results. Filardo et al. studied 49 patients with follow-up that extended up to 60 months postoperatively, the IKDC score was recorded at 24 months and at 60 months postoperatively, at 2 years postoperatively the IKDC score increased from 38.1 to 74.8, the results remained stable over the time, reaching to a level of 76.7 at 60 months follow-up. In the study published Kon et al. in 2016 **(Kon et al., 2016)** on 32 patients with full-thickness cartilage lesions in the patellofemoral joint, who were treated by MACT und followed at 2-, 5-, and 10-year postoperatively. The patients were evaluated clinically by IKDC score and by Tegner activity scale. They showed significant improvement from 46.0 preoperatively to 77.1 at 2 years, 72.0 at 5-years 78.6 at 10 years follow-up, while Tegner activity scale showed enhancement of all subscales from 2.5 to 4.7 at 2 years and 5 years and 4.4 at 10-years follow-up while in the study published by Marlovits et al. **(Marlovits et al., 2012)** on 21 patients who suffered from cartilage lesions at the knee joint after traumatic incidents and followed for 10 years postoperatively, they evaluated their patients clinically by IKDC, KOOS, Tegner activity scale and modified Cincinati score at 1, 2 and 5 years and radiologically with MOCART score at months 3 and 6 and after 1, 2 and 5 years. Significant improvement was found in all subcategories of the KOOS. The IKDC score is improved from 30.1 to 74.3, while the Tegner activity score was improved from 1.8 to 4.3. The MOCART score was also improved from baseline to year 5 from 52.9 to 75.8.

While the results of Siebold et al. **(Siebold et al., 2018) a**nd Roffi et al. **(Roffi et al., 2020)** were superior to our results. In 2018 Siebold et al. **(Siebold et al., 2018)** published a study on 30 patients with follow-up of minimum 3 years, the IKDC to increased postoperatively to 84.2, the 5 subscales of the KOOS were improved. The subjective outcome was not significantly influenced by age, size and location of the defects, which is the same as in our study, while the Lysholm score increased postoperatively to 77.7 and that was inferior to our results.

In the study conducted by Roffi et al. **(Roffi et al., 2020)** published in 2020, they presented the long-term results after MACT in combination with autologous bone grafting in the treatment of juvenile OCD and they followed their patients for 120 months, and evaluated them clinically with the IKDC score, Tegner activity scale und EuroQol- VAS. The IKDC improved from 38 to 83.3, showing slightly better results than ours. In their study the lesion larger than 3.5cm$^2$ obtained

worse results, in contrary to this finding, we found that the patients with lesions larger than 5cm$^2$ had a better IKDC score (84.33), while similar to our findings, they found also in their study that the female patients have worse outcome than the male patients.

The patients included in this study had a mean age of 32.6 years at the time of the MACT, age ranged from 16 to 46 years old. Like described in the literature, we found that here is no significant influence of age of the patients on IKDC score, nonetheless, Rosenberger et al. **(Rosenberger et al., 2008)** found a basic efficacy of MACT in older patients as well, another study by Niemeyer et. al **(Niemeyer et al., 2010)** concluded that the results of MACT in patients 40 years and older were not inferior than that of younger patients, while Gille et al. **(Gille J, 2016)** found that there was no correlation between age of the patients at the time of the surgery and clinical outcome. In our study a total of 10 males (66,6%) and 5 females (33.3%) were treated with multiple MACT. Both men and women achieved significantly better results in the IKDC score at the time of the follow-up compared to the preoperative condition. In the male group, there was more mean improvement in the IKDC in the male group than the female group, similarly, in a follow-up study by Kreuz et. al **(Kreuz PC, 2006**), they found that the female patients with patellar defects have worse outcome. While in the study done by Gille et al. **(Gille J, 2016)** they found no difference in the outcome regarding the gender of the patients. While Filardo et al. **(Filardo G, 2013)** found that females have more unfavorable conditions regarding the activity level, aetiology and site of the lesion, these factors are responsible for the different outcome in the female gender. Preoperatively, the men and women started with different scores, when these scores standardized for each age group, they did not find any gender related differences in the scores.

In our study, the causes of cartilage defects in our patients were diverse, non-traumatic incidents (n=6, 40%), traumatic incidents (n= 7, 46.66%) and OCD (n= 2, 13,33%). We found that there was more improvement in the IKDC score in patients who suffered from cartilage lesions after acute trauma or OCD than old traumatic or degenerative lesions. These findings matches the results of Rackwitz et al. **(Rackwitz et al., 2012)**, as they found in their study that the OCD has better results than traumatic or degenerative lesions after treatment with MACT.

A clear improvement of the results in the IKDC score was shown in our patients at the time of the follow-up in the different localities of the lesions. The localization of the lesion has no significant influence on the IKDC score (p- value is 0.33 using Chi-square test) nor on the MOCART score (p-value 0.52 using Mann-Whitney U Test). As the lesions that we treated in our group were multilocular, we found that the lesions that were located only in trochlea had shown the best improvement in the IKDC score preoperatively from 48.4 to 89.6 (41.2 points of improvement), next to that came the lesions in the patella alone (from 36.2 to 72.6, with improvement of about 36.4 points), then MFC and patella (from 49.3 to 84.2, with improvement of 34,9 points), then LFC and patella (from 51.9 to 81.6 with improvement of 29.7 points), then MFC and trochlea (from 52.9 to 82.4 with improvement of 29.5 points) and lastly the lesions in patella and trochlea simultaneously (from 44.6 to 69.5 with improvement of 24.9 points), also we found that the simultaneous lesions in patella and trochlea had the worse IKDC score with 69.5 points. We suggested that the more improvement we observed in IKDC score in lesions found in the trochlea and patella alone may be due to the low preoperative IKDC value. In our group of patients, we found that the lesions of the trochlea have the best postoperative IKDC score.

Niemeyer et al. **(Niemeyer et al., 2008)** in their research on 95 patients, they stated that the defect size was a major influencing factor on the clinical outcome in treating retropatellar lesion with autologous chondrocyte implantation. They found that smaller lesion had better outcome, also they observed that lesions on the lateral patellar facets had better outcome that those located in the medial facet of the patella or lesions extending to both medial and lateral patellar facets. In 2000, Peterson et al. **(Peterson et al., 2000)** reported results of 101 patients over 2 to 9 years follow-up after treatment with ACT. In the evaluation of the patients, it was shown that, good to excellent results in isolated defects in the femoral condyle in 92% of the patients, in multiple lesions (femoral lesions in combination with lesions of the trochlea or the patella) in 67% of the patients, with osteochondritis dissecans in 89% of the patients, lesions of the patella in 65% and of the femoral condyle in combination with an anterior cruciate ligament rupture in 75% of the patients.

Brittberg et al. **(Brittberg et al., 1994)**, observed after investigating 13 traumatic femoral cartilage defects, 3 osteochondral lesions caused by osteochondritis dissecans, and 7 patellar

cartilage defects with a defect size of 1.6–6.5 $cm^2$ in 23 patients with a mean age of 27 (14–48 years) treated with an ACT for the first time. Two years after the transplant, they found that patients with femoral transplants had good or excellent results. While patients with patellar transplants showed good results in 2 cases and satisfactory or poor results in 5 patients.

In our patients we found that the size of the lesion had no significant effect on the IKDC score postoperatively, the defect size did not significantly influence the clinical outcome, the same was reported by Pietschmann et. al. **(Pietschmann et al., 2009)** and Gobbi et al. **(Gobbi et al., 2006)** who found also that there was no significant correlation between the size of the lesion and the IKDC score postoperatively. Rackwitz et al. **(Rackwitz et al., 2012)** observed that the positive improvement of the IKDC score was also independent of the defect size.
However, the dependency of the postoperative results of the MACT on the defect size is still controversial and must be further targeted using larger numbers of cases and longer follow-up times.

In another large study done by Nawaz et al. **(Nawaz et al., 2014)** over 827 patients who suffered cartilage lesions (421 in MFC, 109 in LFC, 200 Patella, 50 trochlea and 47 multilocular) and have mean age of 34 years (range, 14 to 56 years old), the patients were operated over a period of 10 years with mean follow-up for 6.2 years and evaluated clinically by VAS, Stanmore functional score and modified Cincinnati rating score. They observed that, in younger patients, the graft has longer survival time than in older patients and this matches our theory. Same was stated by De Windt et al. **(de Windt et al., 2009)** who demonstrated better outcome and score in patients 30 years and younger and suggested that this was related to consequences of cell and tissues aging. In contrast to that Niemeyer et al. **(Niemeyer et al., 2010**) reported that the results between patients 40 years and older are comparable with younger patients.

Nawaz et al. **(Nawaz et al., 2014)** found that the graft implanted in the LFC survived longer, with fewer failures, then they noted that grafts transplanted in MFC, Patella or multilocular lesions have higher failure rates. Regarding to the patients who had additional operations in the knee before MACT, 282 patients from their group were previously operated and they have poorer clinical outcome. In contrast to our finding we did not find any significant difference between patients who undergone additional operations to MACT.

Due to varus knees, only 2 patients undergone correction of leg axis using HTO, we found that corrective osteotomy seems to have no significance on IKDC score, or on MOCART score. The indication for HTO in combination with MACT in young patients with varus malalignment and cartilage lesions is primarily to off-load the medial compartment and to transfer the load to the healthy lateral compartment. On the contrary to our finding, Bauer et al. **(Bauer et al., 2012)** found that combining the HTO with MACT has significant improvement on the clinical outcome that was maintained over the 5 years follow-up done with their 18 patients, while they described an initial significant improvement in the MRI results at 12 and 24 months postoperative, this initial improvement was declined at 60 months follow-up.

With regard to the smoking habits, we found that there was no significant influence of smoking habits on both IKDC or on MOCART score, contrary to this finding, Jaiswal et al. **(Jaiswal et al., 2009)** in their study on 129 patients, 66 were nonsmokers, 48 were smokers and 15 were ex-smokers, all their patients were evaluated by modified Cincinnati and Stanmore rating score as well as the VAS before and after the surgery at 6 weeks, 3-6-9 and 12 Months and then on yearly basis postoperative, an arthroscopy was done at 1 year after the operation and a biopsy were taken from the center of the graft to quantify the amount of hyaline cartilage, they found that smoking has a negative effect both clinically and histologically, and that the smokers have lower Cincinnati score and they found that less amount of hyaline cartilage as well as mixture of fibrocartilage is formed in the graft.

Regarding the BMI and in the correlation of the body mass index with the IKDC result, it was found that in our group of patients who had less BMI at the time of the operation had better clinical outcome. This may be related to good preoperative status of the knee before injurty as well as the motivation in the postoperative period and the compliance with the planned physiotherapy plans. This finding matched the results by Jaiswal et al. **(Jaiswal et al., 2012),** they studied the effect of BMI on the clinical outcome on 138 patients and concluded that patients with ideal body weight experienced significant improvement of the symptoms as early as 6 months postoperative that those who suffered from overweight or obesity. It was found also by Mithoefer et al. **(Mithoefer et al., 2005),** in their prospective study found that a lower body mass index was associated with higher scores for the activities of daily living, and worse results were seen in patients with BMI>30 and these results match our results. In contrast to our findings,

Gille et al. **(Gille J, 2016)** found that there is no effect of the BMI on the results on their study done on 38 patients.

For evaluation of the graft repair tissue postoperatively, we examined our patients with MRI at the time of follow-up and we used the MOCART score to evaluate the MRI, in our study, the patients had a mean value of 73.125 points in MOCART score at the time of the follow-up postoperatively (mean Follow-up 37.8 was months), with complete filling of the defect in 60%. Subchondral edema was seen in 44.66% of the implants. These results were inferior to the results published by Aldrian et al. **(Aldrian et al., 2014)**, they operated 16 patients and implanted 23 MACT in focal cartilage lesions grade III-IV according to ICRS, at 10 years the MOCART score was 70.4, complete filling of the defect was 73.9%. Subchondral edema was seen in 86.9% and this finding was worse than ours. But they found no correlation between MRI and clinical outcome and this matches also out finding.

In the literature other studies also used the MOCART score to evaluate the postoperative MRI, and they are therefore comparable to our study in regard to the sub-items like defect filling, integration to the border zone, surface of the repair tissue, signal intensity of the repair tissue, subchondral lamina, subchondral bone edema, adhesions and effusion.

In our study the size of single cartilage defect varied between 2.5 and 6.25 $cm^2$, as every patient has 2 lesions; the average size of the defects per patient ranged from 3.75$cm^2$ to 10.5 $cm^2$. The mean size of the cartilage defects per patient was 7.25 $cm^2$. A total of 30 treated cartilage defects were included in the study. All the treated lesions were either grade III or IV according to Outerbridge classification.

In the examination of the individual findings, a complete filling of the cartilage defect was seen in 18 of the 30 the cartilage defects (60%). In 1 patient only, one cartilage defect was slightly hypertrophied (3.33%). In 4 lesions (13.33%) the cartilage defect was only less than 50% was filled, while in 7 lesions more than 50% of the defect was filled (23.3%).

None of the lesions showed exposed subchondral bones, subchondral edema that is smaller than 1 cm was shown in 65.2% and larger than 1 cm in 21.7%, Our results can be compared with the international literature The MRI results were nearly the same as our results.

Welsch et al. **(Welsch et al., 2011)** and Marlovits et al. **(Marlovits et al., 2006)** found that 65.2% and 61.5% defect filling after 24 months follow-up, that was nearly similar to our results.

In 66.66% of the lesions, the integration of the implant into the surrounding cartilage was also predominantly complete. In 20% of the lesions, the boundary between the implant and articular cartilage was visible ("split-like"). The remaining 13.33% of cartilage defects, they were only partially filled. Marlovits et al. **(Marlovits et al., 2012)** on his study on 21 patients who suffered from cartilage lesions at the knee joint after traumatic incidents and followed for 10 years, stated that the MOCART score in their patients, done at months 3 and 6 and after 1, 2 and 5 years was also improved from baseline to year 5 from 52.9 to 75.8. Their results were nearly the same as our results. They also evaluated the patients clinically by IKDC, KOOS, Tegner activity scale and modified Cincinnati score at 1, 2 and 5 years. Significant improvement was found in all subcategories of the KOOS. The IKDC score is improved from 30.1 to 74.3, while the Tegner activity score was improved from 1.8 to 4.3, which matches also our results.

While Welsch et al **(Welsch et al., 2011)** observed a complete integration of the implant to the surrounding cartilage in about 78% and Trattnig et al **(Trattnig et al., 2006)** observed complete integration in 76.9%, both showed better results than ours.

The assessment of the implants revealed an intact and homogenous surface in 16 lesions (53.33%) as well as a predominantly homogeneous structure of the implant (26.66%, n = 8). 20% (n = 6) showed an inhomogeneous structure. A high degree of destruction of the implant ("cleft formation") was not be observed in any lesion in our study.

While Marlovits et al. **(Marlovits et al., 2006)** described an intact homogenous surface in 69.2% of the patients and this was superior to our findings. Welsch et al **(Welsch et al., 2011)** used an abbreviated version of the score that did not take into account the surface of the implant.

Ebert et al **(Ebert et al., 2011)** studied the clinical and MRI results 5 years after MACT in the knee joint in 41 patients, they evaluated the patients radiologically by MOCART score. MRI showed 89% good to excellent filling of the defects, which is better than our results, while in 67% of the patients showed incomplete filling of the defect, which was inferior to our results.

In our patients, intact subchondral lamina was found in about 24 grafts (80%), while it was not intact in 6 grafts (20%). Subchondral edema was observed in about 46.66% of the grafts (n=14), while in in about 16 grafts (53.33%), no subchondral edema was detected. Evidence of slight adhesions were found only in 4 patients (the lesions were caused by old trauma in three of the patients, while in only one patient followed osteochondritis dissecans). Though, we did not find a clear correlation between this finding and the clinical findings.

Filardo et al. **(Filardo et al., 2014)** observed the effect of subchondral bone edema on the clinical outcome after cartilage treatment, they mentioned in their study that was published in 2013 that the subchondral edema was not constantly present throughout the follow-up period. According to them, the subchondral bone edema was found during the first 2 years of follow-up and then later on it was markedly reduced at the 3$^{rd}$ year of the follow-up and this subchondral edema had no effect on the clinical outcome. In our study we found that the patellofemoral lesions had less edema than other lesions, also we did not find a relation between the presence of edema and the clinical outcome. Our results are nearly identical to their findings.

In a study by McCarthy et al. **(McCarthy H.S., 2018)** to assess the patients clinically by Lysholm score and to evaluate the repair tissue quality either radiologically by MRI or histologically via core biopsy. Mean follow-up was about 8.4 years. They find that the age of patient at the time of the operation did not significantly correlate with clinical outcome. A total of 241 MRI from 136 patients were evaluated using MOCART score, the mean score at the final follow-up was 60, their results were inferior to ours, also with regard to the individual parameters. In the histological examination, the biopsies that were composed only of hyaline cartilage, did not complain of any pain, while at the other side, in patients in which the biopsies contained fibrous tissues, complained of pain.

Possible reasons for the differences between our study and the other studies, mainly related to differences in the duration of the follow-up period, differences in cohort size or cohort composition, the interobserver variability of the individual study centers and differences in MRI device quality.

The influence of the different properties of the MRI devices on the determined MOCART score cannot be excluded regarding manufacturer, coil technology, magnetic field strength (between 1.5 and 3.0 Tesla), type of devices (closed and open), or sequence type (high resolution, intermediate-weighted, fast spin echo, 3D), detailed information on these parameters are not available. The different MRI findings in the various studies cannot currently be explained.

Further studies with more patients using a standardized clinical and radiological evaluation protocols are required to clarify these questions. With regard to the results of MOCART score, a large number of patients reached almost physiological findings at the time of postoperative follow-up, it can be assumed that the MACT has therapeutic efficiency.

**Correlation between the clinical and radiological outcome:**

In our study we found that the IKDC score does not seem to have a significant influence on the MOCART score at the follow-up. Some researches reported correlation between clinical scores and knee effusion (which is MRI finding).

However, the knee effusion must be evaluated cautiously, as the used MRI scoring system, aim to score the graft tissue repair and not on the knee in general, or other knee condition as degeneration.

In systematic reviews by Blackman et al. and de Windt et al., on this topic, one review mentioned that the graft hypertrophy has a very strong relation with the clinical outcome **(Blackman AJ, 2013)**, while the other stated that incomplete filling of the graft repair tissue has correlation with the clinical outcome **(de Windt TS, 2013)**. We observed no correlation between graft infill, signal intensity with clinical outcome. Same finiding were repoted by Ebert et al., Genovese et al., Pietschmann et al., Saris et al. and Takazawa et al. **(Ebert JR, 2011, 2012; Genovese et al., 2011; Pietschmann et al., 2009; Saris DB, 2008; Takazawa et al., 2012),** they have reported that there is no correlation between clinical and radiological outcomes.

Blackmann et al. **(Blackman AJ, 2013)** reported that the consistent correlation between MRI and clinical outcome MRI occur between 6-36 months postoperatively. They suggested that earlier than 6 months, the abnormal findings in the MRI should be considered normal as they are part of the healing or repair process.

Other factors that influence the healing or regeneration process is not evaluated through MRI, as inflammation, nerve growth and vascular penetration. **(Ebert et al., 2014)**

In our study we used the IKDC, KOOS scores, Tegner activity scale and Lysholm score to assess the patients clinically. Tanner et al. **(Tanner SM, 2007)** have reported that IKDC and KOOS scores include the most important items needed in the postoperative clinical examination of the knee. However, some subscales of the KOOS represented some higher importance to the patients more than the others as (Sport/ Rec and QOL subscales), which have shown higher improvement after treatment with MACT.

On the other side, Tetta et al. **(Tetta et al., 2010)** at the time of follow up, found a strong correlation between objective and subjective scores and MOCART score.

Our study has some limitations as small number of patients that can limit the strength of our observations, even though, our findings were comparable to some of the published papers.

There was more than 1 satisfactory statistical finding were found.

We had no histological evaluation of the repair tissue (due to medicolegal limitation), so we failed to compare the clinical, radiological with the histological findings.

| Study | Pietschmann | Rackwitz | Ventura | Zak | Aldrian | Siebold | Roffi | Our study |
|---|---|---|---|---|---|---|---|---|
| **Size of the lesion** | 6cm$^2$ | 5.5cm$^2$ | 4.3cm$^2$ | 3.8 cm$^2$ | 3.8 cm$^2$ | 6 cm$^2$ | 2.8 cm$^2$ | 7.25cm$^2$ |
| **Year of publication** | 2009 | 2012 | 2012 | 2014 | 2014 | 2018 | 2020 | - |
| **MRI** | yes | no | yes | yes | yes | yes | no | yes |
| **Tegner activity scale** | - | - | 4 | 4.4 | 3.3 | 5 | - | 5 |
| **Lysholm** | - | - | 95 | - | - | 77.7 | - | 79.28 |
| **KOOS** | - | - | - | - | - | 78.7 | - | 70.78 |
| **IKDC difference** | 34.8 | 28.3 | - | 27.9 | 14.9 | 38.2 | 45.8 | 31.92 |
| **IKDC postoperative** | 73.6 | 70.5 | - | 69.8 | 59 | 84.2 | 83.8 | 79.80 |
| **IKDC preoperative** | 43.2 | 42.2 | - | 41.9 | 44.1 | 46 | 38 | 47.88 |
| **Follow/ up (Months)** | 24 | 30.2 | 24 | 24 | 120 | 36 | 120 | 37.8 |
| **No. (m/w)** | 32 | 116 | 53 | 23 | 16 | 30 | 19 | 15 |
| **Aetiology of the lesion** | OD/ Trauma | OCD/ Trauma | - | OCD/ Trauma/ Degenerative | - | - | OCD | OCD/ Trauma/ Degenerative |
| **Type of Matrix** | Novocart 3D | Novocart 3D | MACI-Verigen | Novocart 3D | MACI, enzyme/ Hyalograft-C | ACT 3D spheroids | - | Novocart 3D |

Table 10 MACT Studies and the postoperative score values in comparison

# 7 Summary

The aim of this study is the evaluation of the clinical and radiological results in the treatment of full thickness multiple cartilage defects in the knee joint with MACT. The majority of our patients were satisfied after treatment with MACT (86.66%).

In the examined patients', the leg axis, the gender, and BMI seem to have a significance on the clinical postoperative results. Etiology of the lesion is found to be an important factor that had an influence on the intensity of pain. Patients who suffered from osteochondritis dissecans and acute trauma showed significantly better clinical scores than those patients with degenerative cartilage defects.

The age, defect localization, correction of leg axis, size and smoking habits did not show significant influence on the results of the MACT in our patients, while the body mass index has an inverse correlation impact on both IKDC and MOCART score. The females had a lower IKDC score in comparison to the male patients.

## 7.1- Questionnaires:

The questionnaire completed by the patients in the follow-up examinations consisted of "The 2000 IKDC- subjective knee evaluation form" and the "Visual Analog Scale (VAS)", Lysholm score, Knee injury and Osteoarthritis Outcome Score (KOOS) and Tegner activity scale.The "IKDC subjective knee evaluation form" score is a valid score for the assessment of cartilage replacement procedures with high reliability and reproducibility. **(Higgins et al., 2007)**

The evaluation of pain was based on the visual analog scale (VAS), a pain scale with high reliability. **(Langley & Sheppeard, 1985)**

The scores we used in our questionnaire have been described and used in the literature and used to evaluate the cartilage repair procedures. **(Anders et al., 2008; Nehrer et al., 2008; Ochs et al., 2007).** We tried to minimize the questionnaire size to encourage the patients to participate in the study. In the questionnaires used, the status of rehabilitation is missing. Therefore, no statement could be made about the influence of the physiotherapy on the clinical results.

Care should be taken in subsequent studies, to document and include, the type and scope of sports activities of the patients in the questionnaire within the framework of postoperative rehabilitation.

## 7.2- Radiology:

MRI has been considered a very effective non-invasive method for examining the articular cartilage as well as the MACT grafts.

In this study, the patients were postoperatively examined by magnetic resonance imaging in cooperation with the institute of the clinical radiology at Klinikum Rechts der Isar, Technical University in Munich.

With the help of MOCART score, we were able to perform an assessment of the MACT implants using MRI images. All the patients were examined postoperatively by 3.5 Tesla devices. The MRI examination technique was explained to the patients and a written consent was taken from all the patients before examination.

The MOCART Score, published by Marlovits for the first time in 2006, contains many important criteria for the assessment of cartilage transplantation procedures. **(Marlovits et al., 2006)** The score was calculated based on the criteria included in the score. The MACT implants were standardized and evaluated for statistical analysis. This enabled the monitoring of the MACT implants and the documentation of the healing process in the articular cartilage.

A disadvantage of the assessment of the MRI examination was the metallic artifacts that are caused by metal implants or particles. Positions of these artifacts at the implant edge hinder the optimal assessment of certain criteria for example integration, surface, the structure of the implanted membrane as well as the subchondral bone.

Certain criteria as joint effusion and adhesions are fixed criteria in the MOCART score, these criteria were assessed also in our study as consequences of the surgical procedure. And this is especially done in patients who have had additional procedures. Those criteria affected the MOCART score without actually giving any information about the graft or regenerating cartilage.

X-rays were done preoperatively to assess bone condition and to measure the leg axis, postoperatively x-rays were done only to control the bone healing after osteotomy as well as after removal of the plate.

## Conclusion:

We evaluated the clinical and radiological results after treating large multilocular full thickness cartilage lesions of the knee joint by matrix autologous chondrocyte transplantation and we observed that the use of cell-based biological approach (MACT) is an efficient method for the treatment of multilocular large sized full thickness cartilage lesions of the knee. In our group of patients, we found a significance improvement in both the subjective symptoms and objective findings. We could identify the individual factors which influenced the postoperative outcome, the patients with lower BMI at the time of the operation showed significance on both IKDC and MOCART scores, the leg axis showed marginal significance only on IKDC score while the female group showed lower MOCART score than the male group.

Other individual criteria as age of the patients, cause and size of the lesions, knee functions at the examination, smoking habits and the presence of additional operation did not show any significance. Also, we did not find any significant correlation between the IKCD and MOCART scores.

We must also mention that additional studies should be done on larger numbers of patients and for longer periods of follow-up to establish the effectiveness of this treatment method. Also, in the questionnaires used for clinical evaluation of the patients, the status of rehabilitation is missing. Therefore, no statement could be made about the influence of the physiotherapy on the clinical results.

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