AUTOLOGOUS CHONDROCYTE IMPLANTATION FOR CARTILAGE REPAIR

STILL EXPERIMENTAL?

– Written by Mats Brittberg, Sweden

In October 1987, the first human autologous chondrocyte implantation in the world was performed[1]. It is now 26 years since that first example of human musculoskeletal tissue engineering was done but still today, many patients who ask about such an operation are told by their doctors that these operations still are experimental. If this was the case, most of what we, as orthopaedic surgeons, do could be regarded as experimental surgery. Autologous chondrocyte implantation (ACI) has been performed in more than 30,000 patients worldwide since 1987. This paper aims to review the ACI technology.

THE TROUBLESOME CARTILAGE

Cartilage has a poor ability to self-repair after an injury[1]. A large variety of repair techniques for injured cartilage have been developed and used over the last 60 years, from bone marrow stimulations to chondrogenic tissue- and cell-based repairs[2]. Among such techniques is ACI, in which a patient's own cartilage is harvested, followed by cell expansion in vitro and finally re-implantation into a cartilage defect. Results are available with up to 20 years follow-up[3] and a high percentage of the patients do very well, clinically, with relatively few complications.

There are three generations of ACI:

- **1st generation** ACI with a chondrocyte suspension injected under a periosteal flap.
- **2nd generation** ACI with a chondrocyte suspension injected under a collagen membrane.
- **3rd generation** ACI with chondrocytes seeded on or in a scaffold.

For the clinical doctor, the ultimate goal is to treat the patients with cartilage injuries in order to restore the patient's function to the pre-injury state and remove or reduce the pain. So far, no operative technique has been able to fully regenerate destroyed cartilage tissue. However, the results when using a patient's own chondrocytes for the repair has raised the hope that one may be able to re-establish a damaged joint with a high quality functional repair.

INDICATIONS FOR ACI

The ideal patient to be treated with ACI is a symptomatic patient with a full thickness chondral or osteochondral defect surrounded by normal cartilage in a healthy

knee. However, the ideal lesion is more the exception than the rule, as many lesions occur in knees with concomitant pathology and some degree of uncontainment.

As the ACI technology is expensive, the most common indications have been to use ACI as a *second line of treatment after the failure of other simpler cartilage repair methods.*

Furthermore, most of the simpler cartilage repair methods are indicated for small- to medium-sized defects. ACI also performs well for larger defects >3 cm^2 which makes ACI *a primary method of choice for larger chondral and osteochondral defects.*

CONTRAINDICATIONS

ACI is **not indicated** as a treatment option for:

- **Severe osteoarthritis**, such as in the presence of large bipolar (kissing) bone on bone lesions with thin surrounding cartilage. Therefore, in addition to a physical examination, standing anteroposterior 45° bent-knee and patellar alignment radiographs should be obtained to rule out advanced degenerative joint disease.

Other contraindications are:

- Active rheumatoid arthritis.
- Active autoimmune connective tissue diseases.
- Patients with concomitant malignancies.

THE OPERATIVE TECHNIQUE

In the original ACI technique[1], the basic steps for 1st and 2nd generation ACI are as follows. For the 3rd generation ACI, the 1st operation is similar to the 1st and 2nd generation but different in regards the implantation.

Operation 1: Cartilage biopsy harvest

When a cartilage lesion is suitable for ACI, the harvest of cartilage for cell expansion is done trans-arthroscopically from a minor load-bearing area such as the upper medial or lateral upper femoral trochlear area. The notch area is another alternative to use for harvest. About 200 to 300 mg of cartilage is needed for cell expansion at a Good Manufacturing Practice (GMP) cartilage laboratory. Blood is taken from the patient to be processed into serum for cell culture use.

> ***the primary goal of in vitro chondrocyte manipulation is to increase the cell number***

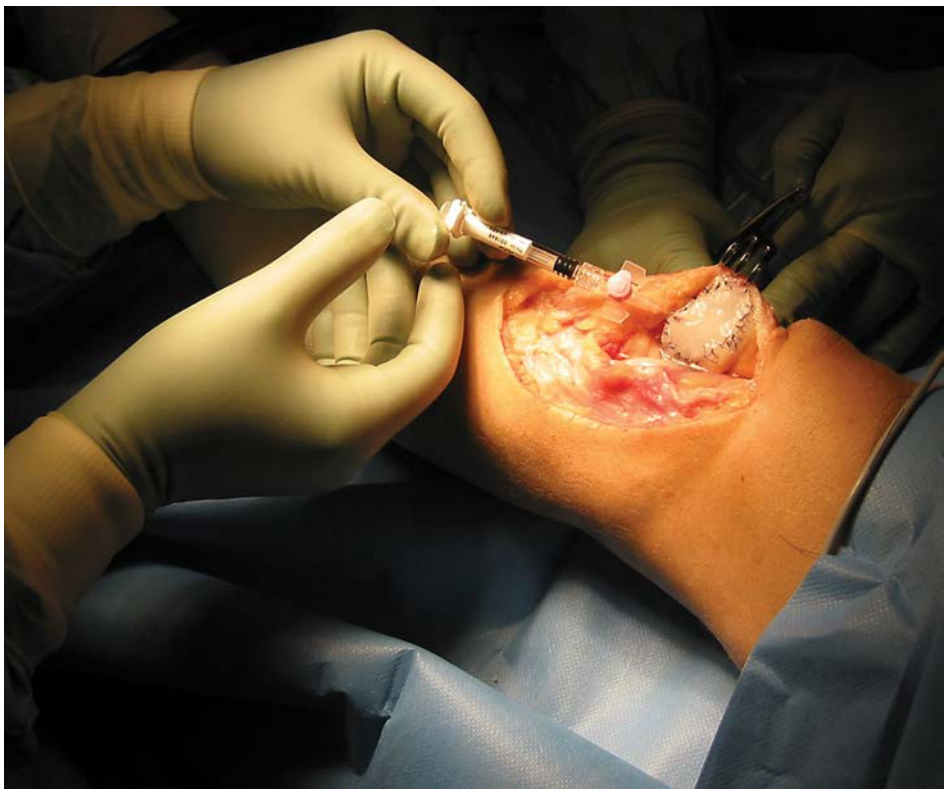


Figure 1: 1st generation autologous chondrocyte implantation with a patella lesion covered by a sutured periosteal membrane. The cultured chondrocyte is in the syringe as a suspension to be injected into the defect under the periosteum.

Chondrocyte in vitro expansion

In vitro cell expansion

To repair cartilage defects, a large number of chondrogeneic cells are needed to simulate the cell condensation seen in embryonic cartilage and joint formation. Subsequently, the primary goal of in vitro chondrocyte manipulation is to increase the cell number. Chondrocytes are isolated enzymatically and expanded in growth medium with autologous serum. After 2 weeks of expansion, cells are trypsinized, washed and re-suspended to a final treatment density of 30 million cells/ml.

If the cells are to be implanted on a membrane or in a scaffold, the process takes longer (around 5 to 6 weeks). After 1 week of cell expansion in monolayer, the cells are seeded on the suitable scaffold.

Operation 2: Debridement of cartilage lesion

It is important to make a careful debridement of the cartilage lesion into healthy, vertical walls of surrounding cartilage. The lesion area should be turned into a slightly oval defect. The size of the defect is measured using a sterile packaging of the sutures as a template.

Operation 2: Cell implantation for a 1st and 2nd generation ACI

For 1st and 2nd generation ACI, the operative procedure has to be done via an open or a mini-open technique. The debrided cartilage lesion is covered by a periosteal flap or an inert collagen membrane. The periosteum is harvested through a separate incision from the proximal medial tibia, just distal to pes anserinus. The periosteum should be sized and cut with a scalpel and harvested sharply with a periosteal elevator, carefully released from the bone. The harvested periosteum should be thin without fibrous tissue. The periosteal flap is placed over the defect with the part that has been attached to the bone; the chondrogeneic progenitor cell containing cambium layer facing towards the cartilage defect.

The flap is sutured to the defect with interrupted resorbable 5-0 or 6-0 sutures. Inter-ruptured sutures are put with an interval of about 3 to 4 mm.

One should aim to angle the suture needle towards the periosteal membrane approximately 2 mm from its edge and pass through the membrane into the adjacent cartilage wall following the curvature of the used needle. Entrance should be about 2 mm below the surface and with a 3 to 4 mm bite. Fibrin glue is used to seal the suture line to minimise leakage of the seeded chondrocytes.

The same suture technique could be used when exchanging the periosteum with a collagen membrane – ACI 2nd generation.

The cultured chondrocyte suspension is injected into the defect below the membrane. A final suture is put at the implantation hole after implantation. The aim is to implant at least 2 000 000 cells/cm^2 (Figure 1).

Operation 2/3rd generation ACI

The 3rd generation ACI is now the most used generation of ACI techniques worldwide. Three variants exist:

- Cell carriers[4].
- Cell seeded scaffolds[5].
- 3D aggregates of chondrocytes without a supporting material[6].

Cell carriers transport the cells on the surface of a collagen membrane, bringing them into the injured site where the cells leave the membrane by cell migration out into a layer of fibrin glue.

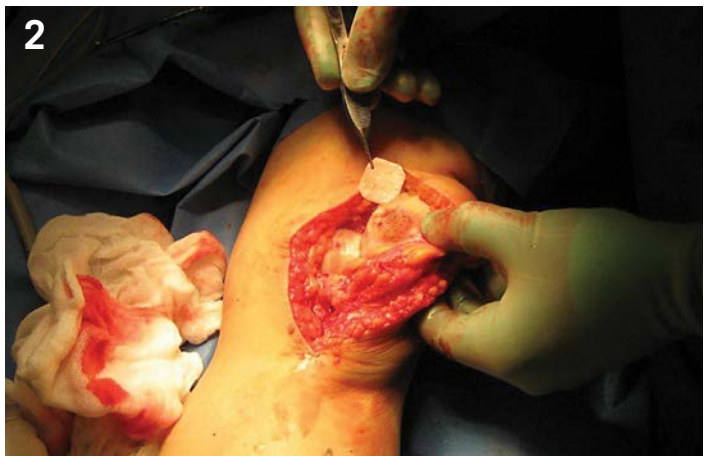
With a scaffold, cells are allowed to migrate into a porous material where they attach and start to produce a cartilaginous matrix. Such scaffolds are either glued into position or fixated with resorbable pins.

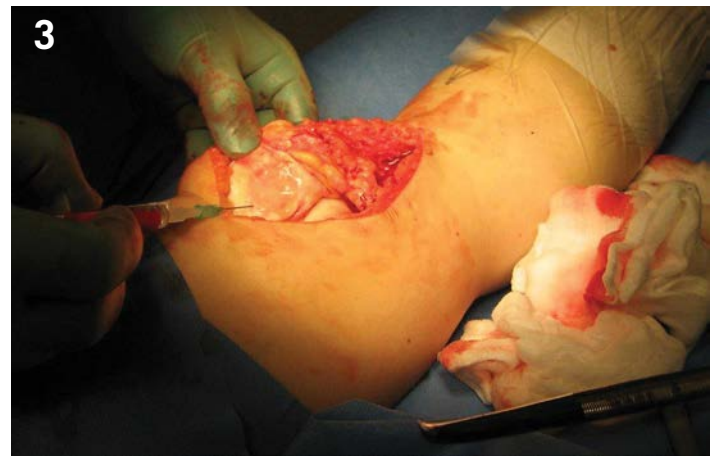
Today, there exists one commercial cell carrier and several types of pure scaffolds and one type of 3D chondrocyte aggregate. The 3rd generation ACI variants are used either via mini-open technique or preferably, trans-arthroscopically.

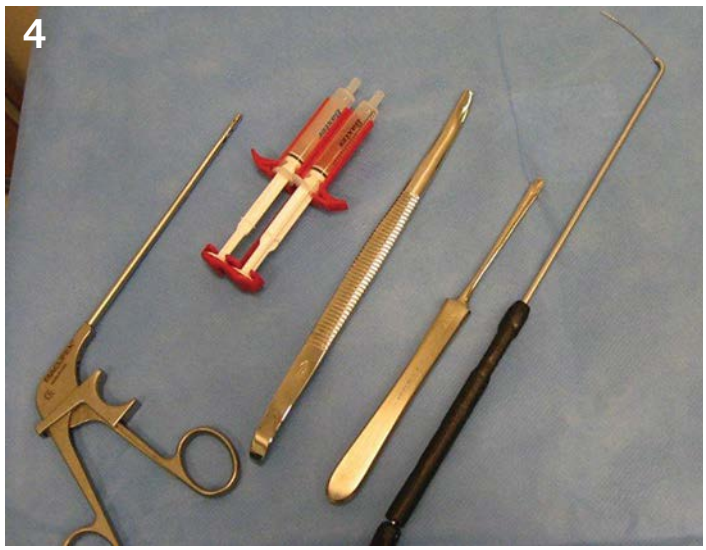
The author currently uses a hyaluronic-based cell seeded scaffold[7] (Figure 2, Figure 3). There are different techniques to implant the cells in such a scaffold – I describe my personal technique below.

My own way

The lesion is debrided as described above (Figure 4). The lesion bottom is covered with a thin layer of fibrin glue injected via an arthroscopic portal. The lesion-sized scaffold is grabbed with a fine grasper and implanted trans-arthroscopically into the lesion (Figure 5) and extra fibrin glue is injected over the scaffold surface. If the







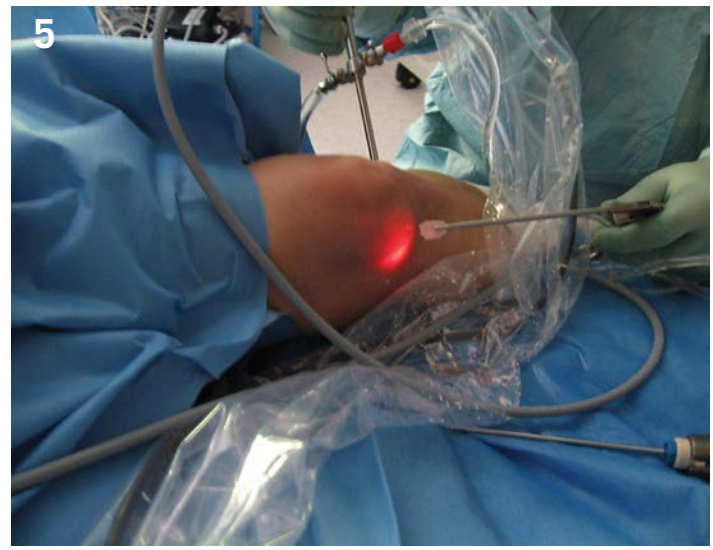


Figure 2: A 3rd generation autologous chondrocyte implantation implant. A cell seeded hyaluronan scaffold has been cut into the right size for a patella defect.

Figure 3: The sized hyaluronan cell seeded graft has been glued into the patella defect.

Figure 4: Suitable instrument set for autologous chondrocyte implantation trans arthroscopic graft implantation. From left, a grasper with plain grasping surfaces, a fibrin glue syringe, a tonsil elevator used to compress the implanted graft and mould the glued surface, a raspatorium used for the sharp debridement of the injured cartilage, a ruler used to measure the defect size for the sizing of the graft prior to implantation.

Figure 5: The grasper is used to introduce the graft into the joint through an arthroscopic portal.

defect is deep, one may have to put more scaffold layers over the initial layer in a 'mille feuilles'-like fashion. The top layer should be slightly below the surrounding cartilage as some swelling of the implanted scaffold is expected. A curved tonsil elevator is used to contour the implanted scaffold to make it fit nicely into the lesion site. The stability of the graft is tested by repeated gentle passive flexion and extension movements (Figure 6, Figure 7).

CONCOMITANT KNEE PATHOLOGY

With any cartilage repair method, good results should not be expected if the coexisting knee pathology is not carefully addressed. Biomechanical malalignment and ligamentous insufficiency can lead to excessive forces and abnormal compressive loads that can damage the repair tissue. It is therefore critical that any associated knee pathology be identified and corrected prior to or in conjunction with the cell implantation. The concomitant knee pathology treatment can be performed in a staged surgical procedure prior to ACI or at the same time as ACI surgery.

BIOMECHANICAL MALALIGNMENTS

Included in the preoperative evaluation of the patient's knee joint are plain X-rays and full-length films from hip to ankle. If the mechanical axis passes through the area in which the chondral injury is located, an unloading osteotomy is recommended to shift abnormal forces away from that area. Unloading osteotomies are also to be considered when the lesions on the femoral condyles are large even without an existing malalignment. As an alternate, an unloader brace may be used to temporarily unload the grafted area during maturation.

Special remarks regarding the patella

Depending on where the lesions are situated on the patella, biomechanical unloading for the lesions may be considered. Lateral release relieves abnormal tilt of

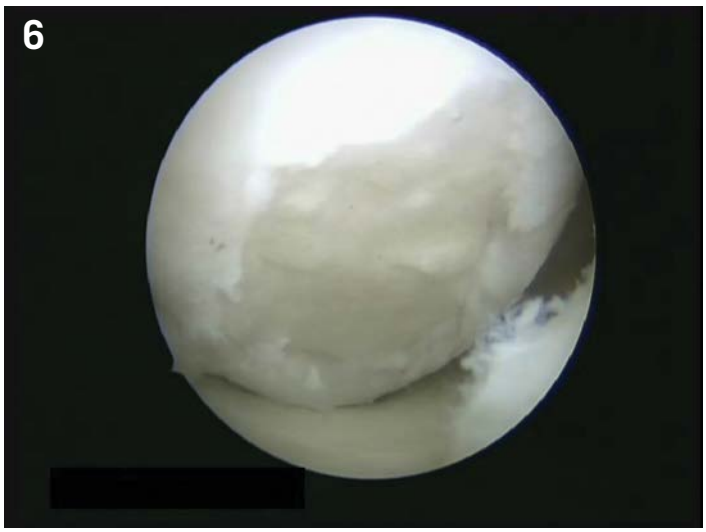
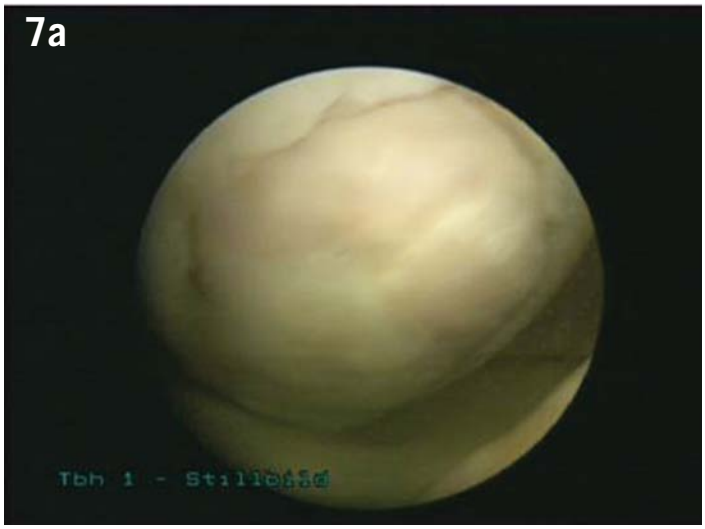
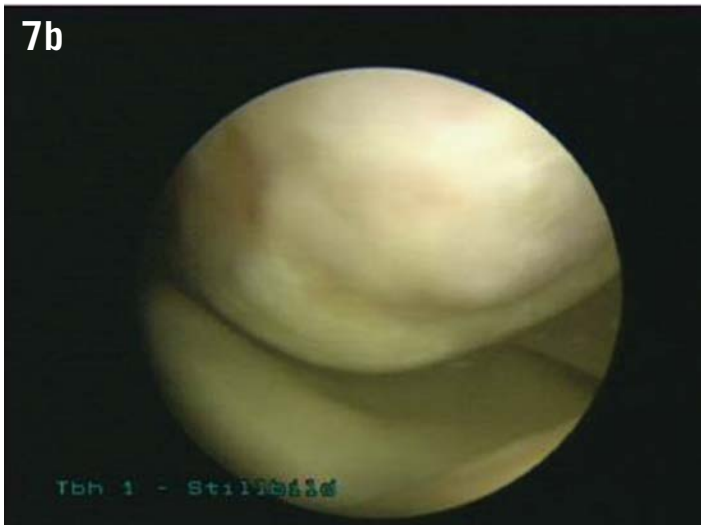


Figure 6: A hyaluronan scaffold has been glued into a femoral condyle lesion.

Figure 7: The cartilage injury seen in Figure 5, treated by a hyaluronan cell seeded scaffold 5 months post-surgery. The left photo shows an upper border zone still not filled with repair tissue. The right photo shows the posterior part of the graft with repaired interzone.





the patella but if there is lateral facet degeneration, osteotomy is also needed.

Key points:

- Distal lateral patellar cartilage damage does well with tibial tubercle anteromedialisation alone.
- Total patellar, bipolar and those with trochlea chondral lesions do poorly with anteromedialisation alone; results are improved when ACI added.
- If bipolar uncontained patellofemoral cartilage lesions with bone erosion exist, the surgeon may consider either prosthetic implantation or osteochondral allografts.

LIGAMENT INSUFFICIENCY

Ligament insufficiency produces excessive shear forces in the knee, which may negatively influence the repair tissue. Anterior cruciate ligament reconstruction should precede ACI if there is a concomitant cartilage lesion to be treated. Regardless of the anterior cruciate ligament and ACI techniques that are used, one should wait for final tibial fixation until the ACI graft has been implanted.

MENISCAL PATHOLOGY

In the presence of a total meniscectomy, or when the meniscal function is equivalent to a total loss, concomitant meniscus allograft transplantation may be considered. When performing a meniscal allograft concomitantly with an ACI, the meniscal allograft should be placed and secured, followed by the ACI grafting.

BONE DEFECTS

The recommendation is to bone graft defects with over 8 mm of bone depth. Bone grafting can be done at the time of arthroscopic evaluation but most often it is done in one stage.

1st and 2nd generation ACI

The ACI is done in combination with bone grafting via the so called 'sandwich technique'; the bone defect is filled with bone grafts from crista iliaca or the proximal tibia. A peiosteal flap is placed on top of the bone grafts, level with the subchondral bone plate. Finally a second periosteal flap is positioned on top of the cartilage defect and a chondrocytes suspension is injected in between the periosteal layers.

3rd generation ACI

The bone defect is first debrided into bleeding bone followed by additional subchondral drilling. The bone defect is then filled with bone grafts impacted into the defect trans arthroscopically with the help of a syringe that has had the tip cut off. Finally, one or several layers of the cell seeded graft are glued on top of the bone grafts.

> ***The ideal patient for ACI is symptomatic with a full thickness chondral or osteochondral defect surrounded by normal cartilage in a healthy knee***

POSTOPERATIVE REHABILITATION

The basic principles of a successful autologous chondrocyte implantation rehabilitation programme are centred on:

- Protection of the graft.
- Mobility and motion exercises.
- Muscle strengthening.
- Progressive weight-bearing.

It is critical to protect the repair tissue from excessive intra-articular forces during the early repair period and especially important to avoid twisting rotational shearing forces. Gradually increased weight-bearing is recommended, with pain deciding the level of weight-bearing.

Early on, the following should be introduced:

- Isometric quadriceps training.
- Straight leg raises for hamstring strengthening.
- A progressive increase of the training to resisted exercises and subsequent return to more and more of normal functional activities.

At **3 weeks**, the following can be introduced:

- Progressive closed chain exercises with light resistance.

At **8 weeks**, the following should be introduced:

- Open chain exercises can be initiated.

Running is not advised until the 8th or 9th month post ACI, with high level activities being initiated in the 12th month.

The contact pressure of the patellofemoral joint is maximised between 40 and 70 degrees of knee flexion, and such angles should be avoided during active knee flexion when lesions in the patellofemoral joint have been grafted until the grafts are mature enough to withstand the shear stresses.

OTHER JOINTS BESIDES THE KNEE JOINT

The ankle joint, shoulder, elbow, hip and wrist are other locations that have been tried in a small number of non-randomised patient studies. With the development of arthroscopic techniques and cell seeded scaffolds, the use of ACI will also be increased in those smaller joint compartments.

CLINICAL RESULTS

Since the report from the first 23 patients in 1994[1], ACI has been performed in more than 30,000 patients worldwide. The clinical results have been reported from numerous centres worldwide.

In a review of 82 published studies, Harris et al[8] evaluated failures and complications from ACI treatments. They found an overall failure rate of 5.8% with a mean time to failure at 22 months. 1st generation ACI had the highest failure rates (7.7%). The lowest failure rates were found for the cell seeded scaffolds and cell carriers (0.83%).

Regarding the long-term fate of ACI, 224 patients were followed up after 1st generation ACI between 10 to 20 years after the implantation (mean 12.8 years)[3]. The mean cartilage lesion size was 5.3 cm^2. There were 92% who were satisfied and would have the ACI again. The Lysholm, Tegner-Wallgren, and Brittberg-Peterson scores were improved compared with the preoperative values. The average Lysholm score improved from 60.3 preoperatively to 69.5 postoperatively, the Tegner from 7.2 to 8.2, and the Brittberg-Peterson from 59.4 to 40.9. Patients with bipolar lesions had a worse final outcome than patients with multiple unipolar lesions.

Vasiliadis et al[9] assessed 36 knees in 31 patients 9 to 18 years after treatment with ACI. All patients had isolated lesions. The knees were clinically evaluated with the Knee injury and Osteoarthritis Outcome Score (KOOS) and the dGEMRIC MRI technique. The quality of the repair tissue was similar to the surrounding normal cartilage, although intralesional osteophytes, subchondral cysts and bone marrow oedema were common. The defect area was restored in most of the studied patients but there was no correlation between the dGEMRIC values and the KOOS outcomes.

Regarding long-term follow up of cell seeded scaffolds, Marcacciet al[5] prospectively evaluated 30 patients (mean age 29.3 years) with full-thickness knee cartilage lesions (<2.5 cm^2) treated with arthroscopic ACI. All patients were evaluated at 2- and 7-year follow-up. The International Knee Documentation Committee subjective score significantly improved from preoperative (34.8) to 7-year follow-up (71.8). The Tegner evaluation showed a significant improvement after the surgery at 2- and 7-year follow-up (from 2.9 to 6.2 and 5.6, respectively). MRI evaluation showed good integration of the graft in the bone and complete maintenance of the grafted cartilage in more than 60% of cases[5].

With a cell carrier, Ebert et al[10] made a prospective evaluation to assess clinical and MRI-based outcomes to 5 years in 41 patients in the knee. A significant improvement (P <0.05) was demonstrated for all KOOS Scores and SF-36 subscales over the postoperative timeline. A significant improvement (P <0.0001) was observed for the MRI composite score, as well as several individual graft scoring parameters. At 5 years after surgery, 67% of cell carrier grafts demonstrated complete infill, whereas 89% demonstrated good to excellent filling of the

12 RCTs w/ ACI Performed from 2003-2013

Eight of them have been studies vs another repair technique

Of those 8 studies, 5 have shown superiority of ACI regarding different outcome parameters vs different repair methods, such as abrasion arthroplasty, mosaicplasty and microfractures

3 studies did not show any differences between studied techniques

3/4 ACI vs MFX studies showed superiority of ACI

Publication	Comparison	Results
Horas et al. J Bone Joint Surg (A) 2003	*ACI-GI vs Mosaicplasty*	=
Schneider et al. Orthop Ihre Grenzgeb 2003	*ACI-GI vs ACI-GIII*	=
Bentley et al. J Bone Joint Surg (Br) 2003	*ACI-GI vs Mosaicplasty*	+
Visna et al. Acta Orthop Belg 2004	*ACI-GIII vs abrasion*	+
Bartlett et al. J Bone Joint Surg (Br) 2005	*ACI-GII vs ACI-GIII*	=
Dozin et al. Clin J Sport Med 2005	*ACI-GI vs Mosaicplasty*	=
Gooding et al. Knee 2006	*ACI-GI vs ACI-GII*	=
Knutsen et al. J Bone Joint Surg (A.) 2007	*ACI-GI vs MFX*	=
Zeifang et al. Am J Sports Med 2010	*ACI-GI vs ACI-GIII*	=
Basad et al. Knee Surg Sports Traumatol Arthrosc 2010	*ACI-GIII vs MFX*	+
Vanlauwe et al. Am J Sports Med 2011	*ACI-GI vs MFX*	+
Brittberg et al. Abstract. Toronto Isakos 2013	*ACI(MACI) vs MFX*	+

Figure 8: Table with the 12 different ACI randomised studies presented. ACI-G1=ACI 1st generation, ACI-GII=ACI 2nd generation, ACI-GIII=ACI 3rd generation. RCT=randomised controlled trial, ACI=autologous chondrocyte implantation, MFX=microfracture.

chondral defect[10]. At 5 years after surgery, 98% of patients were satisfied with the ability of cell carrier surgery to relieve knee pain and 73% with their ability to participate in sport 5 years after matrix-induced ACI[10].

Randomised studies

There are 12 randomised studies[11–22] (Figure 8) done with ACI, 8 of them with ACI vs another repair methodology[11,13,14,16,18,20–22]. In five of those eight studies[13,14,20–22], ACI showed superiority in different clinical outcomes vs the other studied technique (Figure 8). Few other orthopaedic techniques have been so carefully studied but in many occasions, people still talk about ACI as an experimental surgery. This may be because the technology is quite expensive and therefore the requirements for its efficiency are much higher than when using a simple, less-expensive technique like bone marrow stimulation.

CONCLUSION AND FUTURE DIRECTIONS

We are currently working in a new, thrilling era of tissue-engineered repairs for musculoskeletal injuries and a future cartilage repair methodology is likely to be based on either:

- **In vitro developed engineered cartilage tissue or**
- **Intrinsic one stage methods to attract primitive mesenchymal cells from the subchondral bone or neighbouring areas.**

Also interesting is the technique using a delivery of chondrocytes in the form of autologous or allogeneic cartilage tissue fragments in conjunction with an appropriate polymeric scaffolds[23]. Recent studies also indicate possible one stage chondrocyte implantation. A low number of chondrocytes mixed with a larger number of bone marrow mesenchymal stem cells could be induced to proliferate to an increased number of chondrogenic cells needed for the cartilage formation. The future in cartilage repair will subsequently be seen in different methods in how to regulate and direct the chondrogenic cells in order to produce a reliable long-lasting functional repair tissue. ACI is a clinical, well-established method, however it needs to be improved to be able to perfect the repair of cartilage injuries. Subsequently, I can partly agree on the wording 'experimental' but I would prefer 'continuously developmental'.

References

1. *Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N J Med 1994; 331:889-895.*
2. *Mollon B, Kandel R, Chahal J, Theodoropoulos J. The clinical status of cartilage tissue regeneration in humans. Osteoarthritis Cartilage 2013; [Epub ahead of print].*
3. *Peterson L, Vasiliadis HS, Brittberg M, Lindahl A. Autologous chondrocyte implantation: a long-term follow-up. Am J Sports Med 2010; 38:1117-1124.*
4. *Brittberg M. Cell carriers as the next generation of cell therapy for cartilage repair: a review of the matrix-induced autologous chondrocyte implantation procedure. Am J Sports Med 2010; 38:1259-1271.*
5. *Marcacci M, Kon E, Delcogliano M, Filardo G, Busacca M, Zaffagnini S. Arthroscopic autologous osteochondral grafting for cartilage defects of the knee: prospective study results at a minimum 7-year follow-up. Am J Sports Med 2007;35:2014-2021.*
6. *Rössing S, Thermann H, Paessler H, Baum P, Schreyer T. [For discussion-new technique for arthroscopic, autologous chondrocyte transplantation using chondrospheres]. Z Orthop Unfall 2007; 145:276-277.*
7. *de Windt TS, Concaro S, Lindahl A, Saris DB, Brittberg M. Strategies for patient profiling in articular cartilage repair of the knee: a prospective cohort of patients treated by one experienced cartilage surgeon. Knee Surg Sports Traumatol Arthrosc 2012; 20:2225-2232.*
8. *Harris JD, Siston RA, Brophy RH, Lattermann C, Carey JL, Flanigan DC. Failures, re-operations, and complications after autologous chondrocyte implantation - a systematic review. Osteoarthritis Cartilage 2011; 19:779-791.*
9. *Vasiliadis HS, Danielson B, Ljungberg M, McKeon B, Lindahl A, Peterson L. Autologous chondrocyte implantation in cartilage lesions of the knee: long-term evaluation with magnetic resonance imaging and delayed gadolinium-enhanced magnetic resonance imaging technique. Am J Sports Med 2010; 38:943-949.*
10. *Ebert JR, Robertson WB, Woodhouse J, Fallon M, Zheng MH, Ackland T et al. Clinical and magnetic resonance imaging-based outcomes to 5 years after matrix-induced autologous chondrocyte implantation to address articular cartilage defects in the knee. Am J Sports Med 2011; 39:753-763.*
11. *Horas U, Pelinkovic D, Herr G, Aigner T, Schnettler R. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. A prospective, comparative trial. J Bone Joint Surg Am 2003;85:185-192.*
12. *Schneider U, Andereya S. [First results of a prospective randomized clinical trial on traditional chondrocyte transplantation vs CaReS-Technology]. Z Orthop Ihre Grenzgeb 2003; 141:496-497.*
13. *Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg Br 2003; 85:223-230.*
14. *Visna P, Pasa L, Cizmár I, Hart R, Hoch J. Treatment of deep cartilage defects of the knee using autologous chondrograft transplantation and by abrasive techniques - a randomized controlled study. Acta Chir Belg 2004; 104:709-714.*
15. *Bartlett W, Skinner JA, Gooding CR, Carrington RW, Flanagan AM, Briggs TW et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. J Bone Joint Surg Br 2005; 87:640-645.*
16. *Dozin B, Malpeli M, Cancedda R, Bruzzi P, Calcagno S, Molfetta L et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. Clin J Sport Med 2005; 15:220-226.*
17. *Gooding CR, Bartlett W, Bentley G, Skinner JA, Carrington R, Flanagan A. A prospective, randomised study comparing two techniques of autologous chondrocyte implantation for osteochondral defects in the knee: Periosteum covered versus type I/III collagen covered. Knee 2006; 13:203-210.*
18. *Knutsen G, Drogset JO, Engebretsen L, Grøntvedt T, Isaksen V, Ludvigsen TC et al. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. J Bone Joint Surg Am 2007; 89:2105-2112.*
19. *Zeifang F, Oberle D, Nierhoff C, Richter W, Moradi B, Schmitt H. Autologous chondrocyte implantation using the original periosteum-cover technique versus matrix-associated autologous chondrocyte implantation: a randomized clinical trial. Am J Sports Med 2010; 38:924-933.*
20. *Basad E, Ishaque B, Bachmann G, Stürz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. Knee Surg Sports Traumatol Arthrosc 2010; 18:519-527.*
21. *Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP; TIG/ACT/01/2000&EXT Study Group. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med 2011; 39:2566-2574.*
22. *Brittberg M, Saris D, Caron J, Emans P, Kili S, Bezuidenhoudt M et al. Matrix-induced autologous chondrocyte implant vs. microfracture: prospective, randomized trial in European patients, 2-year follow up. Abstract paper 244. 2013 ISAKOS Biennial Congress.*
23. *Cole BJ, Farr J, Winalski CS, Hosea T, Richmond J, Mandelbaum B et al. Outcomes after a single-stage procedure for cell-based cartilage repair: a prospective clinical safety trial with 2-year follow-up. Am J Sports Med 2011; 39:1170-1179.*

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