

Autologous Chondrocyte Implantation

Systematic Review



Ludwig Boltzmann Institut
Health Technology Assessment

Decision Support Document Nr. 034
ISSN online 1998-0469

Autologous Chondrocyte Implantation

Systematic Review



Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, December 2009

Institut for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Projectleader: Priv. Doz. Dr. Claudia Wild

Authors: Martin Künzl

DI Dr. Stefan Mathis

Mag. Tim Johansson

Literature Search: Tarquin Mittermayer, BA(Hons)

External Review: Univ.Prof. Dr. Heinz Redl, Ludwig Boltzmann
Institute for Experimental and Clinical Trau-
matology

Univ. Prof. Dr. Stefan Marlovits, Vienna Me-
dical University, Dep. for Trauma Surgery

Vienna, December 2009

This report should be referenced as follows:

Künzl, Martin; Mathis, Stefan; Johansson, Tim; Wild, Claudia: Autologous Chondro-
cyte Implantation - Systematic Review, HTAProjektbericht, 2009, Nr. 34.

IMPRESSUM

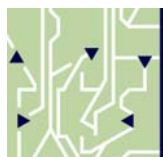
Medieninhaber und Herausgeber:

Ludwig Boltzmann Gesellschaft GmbH

Operngasse 6/5, Stock, A-1010 Wien

<http://www.lbg.ac.at/de/lbg/impressum>

Für den Inhalt verantwortlich:



Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA)

Garnisongasse 7/20, A-1090 Wien

<http://hta.lbg.ac.at/>

Die Decision Support Documents des LBI-HTA erscheinen unregelmäßig und dienen der
Veröffentlichung der Forschungsergebnisse des Ludwig Boltzmann Instituts für Health Technology
Assessments.

Die Decision Support Documents des LBI-HTA erscheinen ausschließlich online und werden der
Öffentlichkeit über den Dokumentenserver „<http://eprints.hta.lbg.ac.at>“ zur Verfügung gestellt.

Decision Support Document Nr. 034

ISSN online 1998-0469

<http://eprints.hta.lbg.ac.at/view/types/dsd.html>

© 2009 LBI-HTA – Alle Rechte vorbehalten

Table of Content

Executive Summary	5
Zusammenfassung	6
1 Autologous Chondrocyte Implantation/ACI	7
1.1 Background & Introduction	7
1.2 Aetiology and Diagnosis	8
1.3 Technical Description of ACI & of Alternative Treatment Options	9
1.3.1 Arthroscopic lavage and debridement	9
1.3.2 Microfracture	9
1.3.3 Mosaicplasty	10
1.3.4 Total knee replacement	10
1.3.5 (M)ACI	10
1.3.6 Post-Intervention: Rehabilitation	11
1.3.7 Follow-up Methods	11
MRI/ Magnetic Resonance Imaging	12
Histology	12
1.4 Scoring Systems for Evaluation	12
1.4.1 Tegner-Lysholm Knee score	12
1.4.2 KOOS/ Knee injury and Osteoarthritis Outcome Score	13
1.4.3 SF36, Short Form 36	13
1.4.4 VAS, Visual analogue score	13
1.4.5 IKDC scoring	13
1.5 Patients & Indications	14
1.6 Regulation and Costs	14
2 Literature Search & Selection	17
2.1 Research Question	17
2.2 Inclusion & Exclusion Criteria	17
2.3 Literature Search	18
2.4 Literature Selection	19
3 Results	21
3.1 Evaluation of Quality of Studies	21
3.2 Presentation of Results	21
3.3 Effectiveness	27
3.3.1 ACI vs. MF	27
3.3.2 ACI vs ACI Methods	30
3.3.3 ACI vs Mosaicplasty (MP)	32
3.4 Results in Systematic Reviews	33
3.5 Safety & Morbidity	36
4 Discussion	39
5 Conclusion	40
6 Literature	41

Figures

Diagram 2.4-1: Quorum tree	19
Figure 3.3-1: Knutsen [44, 45]	28
Figure 3.3-2: Saris [42]	29
Figure 3.3-3: Kon [47]	29
Figure 3.3-4: Visna [48]	30
Figure 3.3-5: Bartlett [43]	30
Figure 3.3-6: Horas [49, 50]	32

Tables

Table 1.2-1: Outerbridge /ICRS classification [5]:	9
Table 1.6-1: ACI-Assessments (see also table 3.4-1).....	14
Table 1.6-2: Reimbursement in selected countries (INAHTA).....	15
Table 1.6-3: Frequency of (M)ACI in Austria	16
Table 2.2-1: Including criteria.....	17
Table 3.2-1: Comparative studies – ACI vs. microfracture	22
Table 3.2-2: Comparative Studies – ACI vs. ACI-C vs. MACI, ACI-C vs. ACI-P	25
Table 3.2-3: Comparative studies – ACI vs. mosaicplasty.....	26
Table 3.4-1: Conclusions from systematic reviews.....	33
Table 3.5-1 Safety and Morbidity	36

Executive Summary

Background: Since 1987, when (M)ACI was first mentioned, the technique has been used all over the world to treat osteochondral lesions in the knee. Nevertheless, the actual effectiveness of this relatively new treatment option is under question: clinical evidence based on controlled trials and long-term follow-up is still missing. For these reasons (M)ACI is being reimbursed in most countries only under research conditions.

Methods: systematic literature search in Medline via Ovid, Embase, Cochrane Library, NHS-CRD-HTA (INAHTA), ISI WEB of Science, WHO Health Evidence Network and Clinicaltrials.gov was complemented by a hand search. Inclusion criteria: Controlled clinical studies with more than 20 patients and a follow-up period of at least one year.

Results: The effectiveness analysis is based on 9 comparative clinical trials and 6 systematic reviews. Within the trials all together 566 patients were treated with mosaicplasty vs. ACI, microfracture vs. ACI, and ACI vs. ACI. The results show consistency and confirm earlier (international) reviews. There is no evidence that ACI or MACI leads to better outcomes in the treatment of osteochondral lesions than any of the alternative treatments. ACI is not superior; at best equal, at much higher cost. The short term (1-2 years) and mid-term (5 years) non-inferiority in highly selected active patients is proven. Long-term data are lacking.

Conclusion: (M)ACI methods must be considered – though often applied - as experimental techniques. The risks of cultivated chondrocyts cannot be ignored and should be given more attention.

(M)ACI is – although in worldwide use – still questioned

systematic literature search complemented by hand searching

9 clinical trials & 6 systematic reviews met the criteria

equality, non-superiority in highly selected pts.

experimental techniques

Zusammenfassung

**klinische Wirksamkeit
der Therapie mit
autologen
Chondrozyten wird
weltweit hinterfragt**

**systematische
Literatursuche,
Handsuche**

**9 Primärstudien &
6 Übersichtsstudien
keine Überlegenheit
nachgewiesen
höhere Kosten der ACI**

**experimentelle
Intervention**

Hintergrund: Erstmals 1987 erwähnt, wird (M)ACI als Therapie von osteochondralen Läsionen weltweit eingesetzt. Als junge Therapieform wird die klinische Wirksamkeit jedoch aufgrund fehlender kontrollierter klinischer Studien und Langzeit Follow-Ups hinterfragt und dementsprechend in nur wenigen Ländern – außerhalb von Forschungsprojekten - refundiert.

Methoden: systematische Literatursuche in Medline via Ovid, Embase, Cochrane Library, NHS-CRD-HTA (INAHTA), ISI WEB of Science, WHO Health Evidence Network und Clinicaltrials.gov, ergänzt durch eine Handsuche. Einschlusskriterien: Kontrollierte Studien mit mehr als 20 PatientInnen und einer Beobachtungszeit von mehr als einem Jahr.

Ergebnis: Die Wirksamkeitsanalyse basiert auf 9 vergleichenden klinische Studien und 6 systematischen Reviews. Die klinischen Studien untersuchten insg. 566 PatientInnen in den Gruppen Mosaicplasty vs. ACI, Microfracture vs. ACI, und ACI vs. ACI. Die Ergebnisse zeigen große Konsistenz und bestätigen frühere systematische Übersichtsarbeiten. (M)ACI ist anderen – etablierten - Intervention gegenüber in der Behandlung osteochondralen Läsionen nicht überlegen. Die Kurzzeit (12 Monate) bis max. mittelfristigen (5 Jahre) Resultate – an hochselektiven sportiven PatientInnen - waren in allen analysierten Gruppen gleichwertig. Gleichzeitig ist (M)ACI deutlich teurer.

Schlussfolgerung: (M)ACI ist weiterhin als experimentelle Intervention – trotz weltweiter Verbreitung – anzusehen. Die Risiken kultivierter Chondrozyten sind nicht zu unterschätzen.

1 Autologous Chondrocyte Implantation/ACI

1.1 Background & Introduction

Autologous chondrocyte implantation (ACI), one of the first cell based therapies, was first trialled in 1987. Since its introduction into clinical practice by Brittberg et al. in 1994 [1], more than 15000 patients have been treated with different ACI techniques. Patients suffering from osteochondral, or chondral lesions, cannot be adequately treated using established treatments. For fifteen years ACI has been believed to lead to better clinical outcomes.

Classical methods are not intended to renew the cartilage itself, but to treat the symptoms of a lesion. However, techniques such as drilling and shaving can lead to osteoarthritis. Microfracture and bone marrow stimulation result in fibrous scar tissue [2], which is different from the normal hyaline cartilage found in knee. Mosaicplasty and the osteochondral auto graft transfer systems (OATS) require autologous cartilage material and can therefore only be used for small lesions. MACI (Matrix associated ACI) – so the expectation - may be able to overcome this problem and renew the hyaluron cartilage tissue.

Early autologous chondrocyte implantation procedures, used a periosteal flap or a collagen sheet to fix the injected cells at the side of lesion [1]. This was the major disadvantage of this first generation of ACI. Due to the need for this additional coverage and debridement, the surgical procedure was not feasible for some cartilages in the knee. To overcome this, new ACI techniques, such as MACI, use a seeded matrix for chondrocytes delivery: This is easier to perform, because there is no need for extra coverage.

As part of the 4th generation of ACI, the use of genetically modified cells, which may be of higher quality, is being tested. However, these investigations have not yet been provided results of clinical relevance. Clinical trials are currently analyzing the impact of diverse bioactive matrices and 3D bioactive matrices on multiple lesion sizes and in different locations.

Nevertheless, many assessments of (M)ACI have been carried out and only a few western countries have decided to reimburse any kind of ACI or to include the procedure in their health benefit catalogues. This paper, based on controlled clinical trials and systematic reviews, aims to compare the outcomes of established/conventional procedures such as microfracture, drilling, and mosaicplasty, with those techniques that use in vitro cultivated cells, such as ACI and MACI. Due to the fact that there are some differences between the treatments and procedures, the major goal of this review is to synthesize the available evidence on patient-relevant long-term outcomes after autologous chondrocyte implantation.

ACI since 1987

**standard therapies:
microfracture,
mosaicplasty etc.**

**development of ACI:
3 generations**

**future research:
genetically modified
cells**

**aim of the paper:
synthesize evidence**

1.2 Aetiology and Diagnosis

aetiology	Traumatic events, as well as several types of arthritis, and spontaneously occurring osteochondritis dissecans (OCD), can lead to cartilage lesions in weight bearing knees. In most cases, cartilages are not innervated, and so primary processes lead only to inflexibility, swelling and, occasionally, mild pain. Therefore the diagnosis is most often confirmed when the diagnosis of ligament injury or disease of the meniscus is made, with both indications often leading to lesions caused by knee instability. Hence, mainly people whose knees are put under stress - athletes and people with an abnormally high BMI - are affected.
children not affected: self-healing capacity	The development of OCD is normally observed during the second decade of a patient's life, while osteoarthritis develops later on, and is rarely found in children and younger adults. Additionally, a self-healing capacity was observed by Messner et al. [3] who reported that previously treated knees became resymptomatic. The patients were symptom-free for 14 years. This long symptom-free period can be explained by the ability of tissue to self-repair.
cartilage repair: 2 forms of cartilage healing	<p>There are two hypotheses of cartilage lesion healing. Both have been observed, but both are poorly understood.</p> <ol style="list-style-type: none"> <li data-bbox="576 981 1377 1070">1. The recruitment of non-cartilage-cells (e.g. some blood stem cells): their ability to penetrate the lesion is called the extrinsic repair pathway, and leads to the softer fibrous cartilage. <li data-bbox="576 1093 1377 1218">2. The intrinsic repair pathway consists of the proliferation of the chondrocytes themselves. In general, due to the restriction of chondrocyte proliferation capacity, the intrinsic pathway, is less effective in the regeneration of symptomatic lesions.
classification for evaluation of articular cartilage defects	<p>Self curing, especially in children and younger adults, has been reported by Prakash et al. [4].</p> <p>Two classification systems have been developed and are generally recommended for the evaluation of articular cartilage defects: the Outerbridge classification and the ICRS (International Cartilage Repair Society) classification. Outerbridge is especially used for patellar defects. The ICRS score – more often used today - was unfortunately hardly used in the analysed trials.</p>

Table 1.2-1: Outerbridge /ICRS classification [5]:

Outerbridge Grade	ICRS Grade	Description
	0	No defects
I	1a	Intact surface, fibrillation, and/or softening, swelling
	1b	Additional lesions on surface
II	2	Lesion-depth to 50% of cartilage thickness, fragmentation and fissuring < 0,5 in. in diameter
	3a	>50%, not to calcified layer, fragmentation and fissuring < 0,5 in. in diameter
III	3b	>50%, to calcified layer
	3c	>50%, to subchondral plate
	4	exposed subchondral bone (any size)

In the following text, the term “lesion” is defined as Grade 3 or 4. This is largely accurate for the patient population analysed in chapter 4.

Even if age, size, BMI, size of bones and physical activity do not differ, there is still a variability of cartilage thickness in the knee of 16-31 % [6] depending on the gender.

gender-specific variability of cartilage thickness

1.3 Technical Description of ACI & of Alternative Treatment Options

1.3.1 Arthroscopic lavage and debridement

Debridement is the medical removal of a patient's dead, damaged, or infected tissue to improve the healing potential of the remaining healthy tissue. Lavage (“to wash out”) is carried out with a saline solution and removes the inflammatory mediators and any cartilage debris residing in the synovial space. This intervention is the first part of all procedures described in this report, and Lavage can be used as a therapy on its own [7]. Additionally often drilling, shaving or any other kind of mechanical treatment is applied in clinical practice.

removal of damaged tissue via “lavage”

1.3.2 Microfracture

The aim of this technique is to fill lesions with fibrous cartilage. A debridement to the subchondral bone plate, followed by the drilling of multiple holes is carried out. Microfracture is one marrow stimulating therapy among others, which use cell recruiting channels, such as prairie drilling and abrasions-arthroplasty. Microfracture is currently the most frequently used technique, due to a lower rate of adverse events such as burning of the tissue and its high efficiency and low costs compared to other techniques. Microfracture is largely restricted to lesions smaller than 4 cm in diameter and for patients with a BMI below 30kg/m². As reported for ACI technique, there is a correlation between clinical effectiveness and BMI [8].

marrow stimulating therapies: microfracture, prairie drilling, abrasions-arthroplasty

**five years average
lasting effect**

Long-term clinical results show that the cartilage becomes resymptomatic after about 5 years, due to the fibrous cartilage [9]. This therapy is often compared to ACL. The hospitalisation period is short and the method is performed arthroscopically. This treatment has been reported to lead to hyaline cartilage regeneration especially in children and young adults. Isolated cells of MFX treated cartilages showed disappointing expression of typ II collagen and osteocalcin, a marker for mineralization and bone formation.

1.3.3 Mosaicplasty

**hyaline cartilage fills
the lesion**

In order to regenerate weight bearing cartilage, it can be useful to transplant a non weight bearing part of another cartilage to the site of the lesion. Mosaicplasty uses this technique. Mosaicplasty, first trialled in 1993 [10], is limited to lesions between 1 and 9 cm². Mosaicplasty has shown to lead to the development of hyaline cartilage in a high proportion of patients. This type of transplantation technique is also used to treat younger patients. Another techniques used in younger patients is osteochondral cylinder transplantation (OCT).

1.3.4 Total knee replacement

**frequently in elderly
patients, because of
unsatisfying long-term
results**

The knee is replaced by an artificial knee. There are several side effects, including swelling, inflammation and pain. Total knee replacement is recommended for older patients only, as the long-term results of the intervention are disappointing. However, the development of new materials suggests that there could be long lasting prostheses which could be transplanted in younger patients without risking the need for further treatment. This method is the most cost intensive and is associated with long hospitalisation periods.

1.3.5 (M)ACI

Common steps

(M)ACI/ (matrix-induced) Autologous Chondrocyte Implantation is a multistep procedure, which varies according to the technique used. All techniques involve the same basic steps [11]:

1. harvesting of cells

Harvesting of cells: The cells are commonly harvested from another healthy non-weight-bearing cartilage tissue, while arthroscopy is performed.

2. cultivation of cells

Cultivation of cells: This step is the most flexible part of the therapy, as the cells react to millions of different signals. Each signal is processed in a different way, and so each molecule, each temperature shift, and every shift in pressure is able to change a cell completely. The quality of a cell-based therapy can be regulated in this step. Usually, the patient's blood is taken, and the serum is isolated, to serve as nutrient medium. The addition of a mixture of differentiation factors is controlling the cells quality. Further it is obvious that every viral contamination, or contamination by intracellular organisms, leads to unexpected and dangerous effects when cells are implanted.

ACI-P and ACI-C

After debridement the cell suspension is injected in a specially created lid of periosteum (ACI-P) or in an artificial collagen lid (ACI-C). This is then sealed by fibrin glue and fixed in place.

In ACI-P, P stands for Periosteum, a flap of which covers the sheet. This is taken from the *proximal tibia*, below the *pes anserinus* [2]. In ACI-C, a collagen layer is used as a cover. ACI is performed using an open surgical procedure.

In the last step, the sheet is fixed. It covers the lesion and, depending on the protocol, is sealed by the second layer. The sheet is screwed or sutured, depending on position and procedure, to the next healthy cartilage, or to bone.

3. reproduction & multiplication of cells on scaffold material

4. reimplantation, fixation

MACI

The cells are loaded upon a collagen layer, and then are positioned arthroscopically to the lesion. There it is sealed and sutured.

matrix-based

Generations of ACI

Due to technological developments, we are able to distinguish between different generations of ACI [12].

The 1st generation of ACI refers to ACI-P, the Brittberg method, [1, 13, 14]: the cover sheet consists of a Periosteum flap.

The 2nd generation is ACI-C: a collagen is used as a cover.

The 3rd generation: a bio matrix, seeded in a 3D way (MACI), is used and performed arthroscopically.

The 4th generation (not of clinical relevance today): different genetical methods, like knockout, knockdown and reprogramming are considered. Furthermore, scaffold free implants are currently being tested on sheep [15].

technological generations of ACI

aims/ intentions/ expectations of technological generations of ACI

1.3.6 Post-Intervention: Rehabilitation

Mostly rehabilitation programs are based on different phases of wound healing. Restrictions on weight-bearing and range of motion are given at the first 2 weeks. After this non-weight-bearing period, the weight-bearing increases slowly, till after 1-2 months the full weight-bearing and full motion range is permitted. Physiotherapeutic interventions and non-knee loading sports like swimming are recommended. The detailed program is depending on the position of the lesion.

weight-bearing & range of motion

1.3.7 Follow-up Methods

Several methods are used to evaluate the results of the different medical interventions used to treat cartilage lesions: radiology, histology and clinical evaluation of the patient's functional state. Here we are showing the two most frequent control assays, MRI as a non invasive method and histology, which is requiring a tissue sample.

evaluation of state of healing

MRI/ Magnetic Resonance Imaging

problems with direct
compare

MRI allows precise measurement of the thickness and surface of soft tissue. MRI is a way of diagnosing early stage cartilage degeneration and preoperatively distinguish between articular cartilage, fibrocartilage, and fluid [16], and can be used in the long term evaluation of patients' development [17].

MRI is one of several follow-up procedures commonly used to measure the results of the effects of MACI. The correlation between MRI and histology outcomes is reported to be high for ACI-treated patients [18], as much as the correlation of clinical outcome and MR imaging in MF and ACI is reported.

Nevertheless, due to varied and non-standardized protocols, MRI has limitations.

Histology

To collect the specimen a control arthroscopy is performed. This is the reason why there is a shortage on healthy samples. This flaw is not given in case of an adverse event, which makes a second look arthroscopy necessary. The staining of the samples makes the cell pattern visible, according to the used stain.

1.4 Scoring Systems for Evaluation

Several scoring systems are used to evaluate patients' functional outcome and quality of life/ QoL.

1.4.1 Tegner-Lysholm Knee score

measures pain &
functioning
of knee

The Lysholm Knee scale is a scoring system consisting of eight questions. There is a maximum of 100 points, and a minimum of 0 points. The categories and maximum points are:

1. Pain; 25 points
2. Instability; 25 points
3. Swelling; 10 points
4. Limp; 5 points
5. Stair climbing; 10 points
6. Squatting; 5 points
7. Use of support; 5 points
8. Locking; 15 points

The lack of a sports category reflects the fact that it was originally developed to validate the outcomes in older patients. Evaluation is usually completed using the Tegner activity scale, with a maximum of 10 points [19]. There is evidence that patients and professional physiologists respond differently to the Lysholm score, especially in the swelling category [20]. The minimum detectable change for the Lysholm scale was 8.9 and 1 for the Tegner activity scale.

1.4.2 KOOS/ Knee injury and Osteoarthritis Outcome Score

The KOOS consists of five categories, with a maximum of 100 points per category. They are:

**pain & symptoms,
but also ADL & QoL**

1. Symptoms
2. Pain
3. Activities of daily life
4. Sports and recreation
5. Knee related quality of live, QoL

The scores within the subclasses may be considered alone, or summed to obtain an overall score. It is assumed to be a valid scoring system for ACI [21]. KOOS is often reported as an average value of all subclasses. Individual category scores are only reported when they are different from the average result.

1.4.3 SF36, Short Form 36

The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. It uses different subclasses to investigate the overall state of the patient [22].

**multi-purpose generic
instrument for
measuring total state of
patient**

1.4.4 VAS, Visual analogue score

The VAS is used to measure non-discrete parameters such as pain. Pain does not appear in discrete categories to patients. The VAS uses a 100 mm “scoring ruler”, where 0 mm represents perfect health [23].

measuring pain

1.4.5 IKDC scoring

The IKDC (International Knee Dokumentation Committee) scoring system has 7 categories. Answers are given by the patient.

**pain & symptoms,
but also ADL**

1. personal data and natural history of disease
2. acute disease
3. daily activities, including sports
4. pain
5. swelling
6. sports
7. function

100 points represents perfect health and the minimum score is 0. Since 2000 a second, almost identical, IKDC rating system has been used, but both are nearly equal in outcome [24].

1.5 Patients & Indications

**young adults,
physically active,
BMI**

Autologous chondrocyte implantation is restricted to non-inflamed and non-genetic diseases of the knee. These restrictions are related to the ability of cells to divide and differentiate and therefore are depending on the cells age. The patient's activity and BMI is of importance - fatty tissue is absorbing different factors, and hormones, leading to an unresponding system – for the selection of the patients. The factor age is discussed controversial. It is reported, that patients over 45 show similar results as younger patients described in literature [25]. Aging itself leads to several developments. It is necessary to mention that the decrease of range of cellular development option, the lower hormone response and the lower hormone level are statistical facts. Depending on the individual patient, this therapy form is recommended for active patients, and so for patient of younger cellular behaviour, but not to younger patients only.

**location & size
of lesion**

Lesions of the lateral or medial femoral condyle, of the trochlea, and also those of the tibial plateau and patella are said to be treatable using ACI techniques. Mostly, the lesions are the result of traumatic events. However, there are also clinical trials on patients with Ahlback syndrome, patients suffering from Osteoarthritis dissecans [26] and osteoarthritis patients. Osteochondral lesions with 1 cm in diameter, as it is reported to be the limit of self curing [9], to 12 cm² may be treated.

1.6 Regulation and Costs

**many assessments in
many countries**

(M)ACI has been evaluated over many years in many countries:

Table 1.6-1: ACI-Assessments (see also table 3.4-1)

Country/ Agency	Year of publication	Conclusion of assessment
France/ HAS [27]	2005	As there are insufficient comparative trials with a good level of evidence or long-term follow-up, ACI is an emerging technique still very much in the development stage.
Spain/ AVALIA [28-30]	2005, 2008, 2009	2005: There is no evidence showing that ACI is better than other procedures on the treatment of chondral lesions of the knee. With the available information, ACI is a safe procedure. 2008: No evidence that ACI is more effective than other conventional techniques in treating chondral lesions of the knee. 2009: only "guided use" (under conditions such as documentation)

Country/ Agency	Year of publication	Conclusion of assessment
Great Britain/ NCCHTA & NICE [31, 32]	2001, 2005	2005: ACI should not be used for routine primary treatment. All patients receiving ACI should be enrolled in ongoing or new clinical studies.
Scotland/ NHS QIS [33]	2005	There is insufficient evidence at present to say that ACI is cost-effective compared to microfracture or mosaicplasty.
USA/ BCBS USA/ ECRI [34, 35]	2003 2004	Not any more available Commercial source, assessment not free available
Sweden/ SBU [36]	2000	No evidence
Germany/ KBV & G-BA [37-39]	2002, 2008, 2009	2002: No evidence 2008, 2009: Since there is no evidence, no general reimbursement. ACI will be re-assessed next time in 2014

Based on several assessment by national HTA-agencies, most countries have decided not to reimburse (M)ACI on a general basis, but to leave the intervention in the research context or allow limited “conditional” use.

**most often
“research only”**

Table 1.6-2: Reimbursement in selected countries (INAHTA)

Norway	Research only
France	Research only
Canada	Research only
Australia	Research only
Israel	Research only
England	Research only
Germany	Research only (KBV: next evaluation in 2014)
Denmark	Status “developmental”, only in specific centres
USA	Reimbursed on basis of individual decision
Italy	Reimbursed (to the level of standard knee operation € 3.022.-)
Spain	Reimbursed, since 2009 “guided use”
Austria	Reimbursed
Belgium	Reimbursed

Austria is one of the few countries in which ACI was included in the benefit catalogue relatively early. (M)ACI, including explantation, cultivation and implantation of cells, has been reimbursed within the Austrian DRG-system for many years (tariff about € 6.000.- to 7.000.-). (M)ACI has been carried out between 132 (2006) and 193 (2003) times a year, though less frequently in recent years.

**Austria: in the
reimbursement
catalogue for
many years**

Table 1.6-3: Frequency of (M)ACI in Austria

MEL 6705 for ACI

	2003	2004	2005	2006	2007
Burgenland	0	0	0	0	0
Carinthia	1	0	0	0	0
Lower Austria	70	26	38	26	25
Upper Austria	46	57	24	24	33
Salzburg	5	16	10	14	13
Styria	22	26	23	30	54
Tyrol	10	10	13	7	6
Vorarlberg	4	1	0	4	0
Vienna	35	69	50	27	12
Austria	193	205	158	132	143

2 Literature Search & Selection

2.1 Research Question

- 1.) Are variable ACI methods a safe and effective alternative compared to established (MF, MP etc.) techniques for the treatment of cartilage defects?
- 2.) Is there an influence of nouvelle technique/recent generations on effectiveness or safety?

PICO-Question

2.2 Inclusion & Exclusion Criteria

The criteria for including relevant studies are described in table 2.2-1.

Table 2.2-1: Including criteria

Population	Patients with grade 3 or 4 cartilage lesions in knee
Intervention	Cell based procedures or products
Control intervention	Natural history, placebo, microfracture, mosaicplasty, abrasive techniques, ACI of earlier generation, total knee replacement
Outcomes	<p>Effectiveness</p> <ul style="list-style-type: none"> • Functioning of knee • Pain • ADL/ Activities of Daily Living • QoL/ Quality of Life <p>Safety</p> <ul style="list-style-type: none"> • Revisions/additional treatments • Adverse events
Studies design	Comparative (randomised and non-randomised) clinical trials (more than 20 patients) Systematic reviews

Publications/ trials were excluded, if

- ✿ they involved fewer than 20 patients
- ✿ they had a follow-up period of less than one year
- ✿ they were non-comparative, only observational

2.3 Literature Search

systematic literature search in databases & networks

The systematic literature search was performed on 01.07.2009. The following databases were searched:

- ✿ Medline via Ovid
- ✿ Embase
- ✿ The Cochrane Library
- ✿ NHS-CRD-HTA (INAHTA)
- ✿ ISI Web of Science
- ✿ WHO Health Evidence Network
- ✿ Clinicaltrials.gov

limitation of search 1987- 2009

The search was limited to the period 1987-2009 and to English and German publications in Medline. All other databases had no language limits. After elimination of the duplicates there were 275 hits. The exact strategy is available from LBI-HTA. The search strategy was complemented by a manual search in scopus.com, ncbi-pubmed, Cochrane, WHO Health Evidence Network, and clinical trials by another investigator. 28 further matches were found.

2.4 Literature Selection

Literature was selected according to the protocol/ PICO presented below. Two researchers independently selected the articles. In case of different views, consensus was found through discussion.

2 researchers involved in selection process

After elimination of the duplicates 275 articles were identified in the search and 206 were excluded because they covered the incorrect topic. 15 were not available as full text and 39 were classified as background literature.

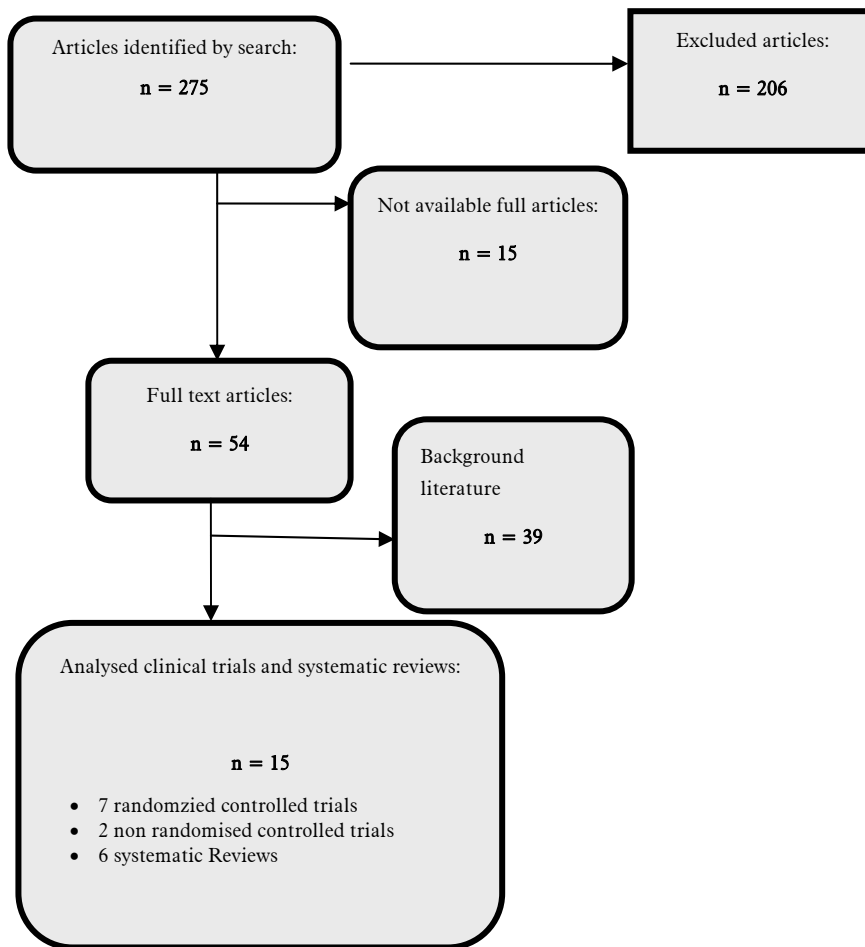


Diagram 2.4-1: Quorum tree

The studies of Brittberg [1] and Peterson[40] are considered as background literature, due to the fact that they are not comparative. However they are the largest clinical studies, with a follow-up of up to 10 years.

3 Results

3.1 Evaluation of Quality of Studies

The quality of the studies was evaluated based on transparency in reporting (randomization method, base line data, drop-outs, sponsoring) and other factors as described in the LBI-HTA methods manual [41]. The quality ratings of the studies (excellent, good, fair, poor) are shown in the extraction table.

Data extraction was done by one reviewer. A second researcher checked the correctness of the extraction. Where interpretations of the texts differed, consensus was found through discussion.

**reporting trials:
randomization method,
base line data, drop-
outs, sponsoring**

**2 researchers involved
in extraction process**

3.2 Presentation of Results

The results of the trials included are presented in tables 4.1-1 to 4.1-3 below: 4 trials comparing ACI with microfracture, 2 trials comparing various generations of ACI with each other, and 3 trials comparing ACI with mosaicplasty were included. None of the 9 comparative trials were rated as excellent. 2 were rated as good [42, 43], 6 as fair [7, 44-50] and 1 as poor [51]. 2 authors Knutsen et al. [44, 45] and Horas et al. [49, 50] published papers on the same patients for 2 different follow-up periods.

**9 comparative trials:
7 randomised,
2 non- randomised**

The results and conclusions of 6 systematic reviews are presented in 4.5-1. The systematic reviews include largely the same trials and therefore only the key results are given.

6 systematic reviews

Table 3.2-1: Comparative studies – ACI vs. microfracture

Author/Year	Knutsen 2004 [44], 2007 [45]	Saris 2008 [42]	Kon 2009 [47]	Visna 2004 [48]
Country	Norway	Belgium, Netherlands, Germany Croatia	Italy	Czech Republic
Study Design N of centres	RCT, MF vs. ACI 4 centres	RCT, MF vs. CCI (non-inferiority) 13 centres	Prospective nonrandomised CT, MF vs. ACI 2 centres	RCT, ACI vs. abrasive technique (Johnson) 1 centre
Sponsor/ product used	Norwegian Ministry of Health Genzyme	TiGenix NV/ ChondroCelect	Hyalograft C	Baxter
Patients age/ sex N pre-treatment (surgical interventions) Aetiology of defects	18-45 yr (Ø 33.3: 31.1), 60% male pre-treated: 94 %, (I: 1.6: C: 1.4) trauma (65%), osteochondritis dissecans (28%)	18-50 yrs (Ø 33.9: 33.9) male: 61% : 67% pre-treated: 88%: 77%, ≥ 37%: 21%	16-60yr (Ø 29.0: 30.6) male: 64.3%: 76.6%: pre-treated: 47.5%: 25%, trauma (56.3%), microtraumatic degeneration (38.75%), and osteochondritis dissecans (5%)	18-50 yr (Ø 29.4: 32.2) male: 72%: 64% male pre-treated: 89%: 80% trauma (86%) osteochondritis dissecans (12%)
Size of lesion	5.1: 4.5 cm ²	2.6 ± 1.2: 2.4 ± 1.0 cm ²	2.2: 2.5 cm ²	4.08 (2-10): 3.36 (2-8.8) cm ²
Indication (inclusion)	2-10cm ² after debridement, osteochondral lesions, isolated Outerbridge grade-3 or 4 defect on medial or lateral femoral condyle or trochlea, knee is stable, normal standing radiographs performed	Symptomatic cartilage lesions of the femoral condyle, lesions between 1-5 cm ² ,	Grade 3 or 4 chondral lesions of femoral condyle or trochlea from 1-5 cm ²	2.0-10.0 cm ² full thickness cartilage defect, caused by trauma, Ahlback syndrome, osteoarthritis dissecans, medial femoral condyle, lateral femoral condyle, tibial plateau, patella
Contraindication (exclusion)	Rheumatoid Osteoarthritis, overweight, malalignment with 5° valgus or varus compared with normal, patella-femoral instability, Bechterew syndrome, chondrocalcinosis, gout	Advanced osteoarthritis, known allergies (penicillin and gentamicin, multiple severe allergies), complex ligamentous instability of the knee, Meniscal transplant, Meniscal suture, Meniscal resection, varus or valgus malalignment exceeding 5°, pre-treatment's: mosaicplasty, microfracture performed less than 1 year before baseline, hyaluron acid intra-articular injections into the afflicted knee within the last 6 months, osteoarthritis drugs, corticosteroid therapy, chronic use of anticoagulants, uncontrolled diabetes, osteochondritis dissecans (recent) (within 1 year before baseline); Etc.	Patella or tibial plateau lesion, diffused arthritis, bipolar lesions, knee instability, axial deviation, infective, tumor, metabolic, inflammatory pathologic changes	n.r.
N Patients (I: C)	80 (40:40)	118 (57:61)	85 (43:42)	50 (25:25)
Pts lost to follow-up, drop out	13 (16%)	59 (50% are missing at 18 months)	5 (5.2%)	0 (0%)
Duration of Follow-up	2004: 24 months (2004) 2007: 60 months (2007)	18 months	60 months	12 months
Outcome measures/ scores used	ICRS, VAS, Lysholm, Tegner, SF-36	Overall KOOS (ADL, Pain, symptoms/stiffness, QoL)	IKDC obj. & subj., Tegner score,	Lysholm knee score, IKDC subj., Tegner, ICRS

Results

Outcome KOOS pre/post (I: C)	n.m.	56.30/74.3:59.53/75.04	n.m.	n.m.
Outcome IKDC subjective pre/post (I: C)	n.m.	n.m	42 (29-50)/ 84 (63.5-99.5): 40 (30-50) / 70 (60-80)	41.28 (11-58) / 76.48 (45-96): 45.00 (20-61) / 68.06 (35-81)
Outcome IKDC objective pre/post (I: C)	n.m.	n.m	15% normal & near normal / 90%: 2.5% / 75%	
Outcome pain pre/post (I: C)	2004 & 2007: 54/32/30/28:54/35/28/26	62.05/79.55:65.47/81.20	n.m.	
Outcome Lysholm function pre/post/FU (I: C)	2004 & 2007: 58/70/72/78: 55/77/75/78	n.m.	n.m.	47.60 (19-43) / 86.48 (57-100): 52.6 (30-68) / 74.48 (51-91) Good/excellent 72%: 40%
Outcome Meyer pre/post (I: C)	n.m	n.m	n.m.	n.m.
Outcome Tegner (preinjury) pre/post (I: C)	2004: n.r. 2007: 3.28/4.05: 3.16/4.36	n.m.	7/6: 7/5	(7.85), 3.23 /5.92: (7.10), 2.30 /4.20
Outcome Cincinnati pre/post (I: C)	n.m.	n.m.	n.m.	n.m.
Outcome VAS pre/post/FU (I: C)	54/40/35:54/35/32	n.m.	n.m.	n.m.
Outcome SF-36	2004 & 2007: ACI: no improvement in SF-36, MF: significant improvement	n.m.	n.m.	n.m.
Diagnostic controls (MRI, histology, arthroscopy, histomorphometry)	histology (H&E staining), arthroscopy more hyaline in ACI	histology at 12th months (H&E, Safarin O, anticollagen II AB), histomorphometry (ratio Safarin: collagen), CCI better scoring in structural regeneration of cartilage tissue/ quality of tissue restoration.	No	histology at 3-5 months: anticollagen ≥ AB, no unspecific staining, arthroscopy
Failure	2004: 2 (5%): 1 (2.5%) 2007: 9 (23%): 9 (23%) - total knee replacement 2/5% per group,	1 (1.8%): 2 (3.3%)	1 (2.3%): 1 (2.4%)	n.r.
Side effects/ adverse events	2004: ACI: reoperation (10 = 25%) because of tissue hypertrophy, psoriatic arthritis (1) MF: debridement reoperation (4= 10%), arthrofibrosis (1), no thrombolytic event, no deep infection 2007: additional shaving or trimming ACI: 10/ 25%, MF 7/17.5%, ACI (1) shaving or trimming (4) MF: additional high tibial osteotomy (1), additional microfracture (5), mosaicplasty (2),	AEs 88%: 82% Severe AE 12%: 13% Frequent: arthralgia (35/57 CCI, 35/61 MF), joint swelling (11/57 CCI, 3/61 MF), joint crepitating (7/57 CCI; 1/61 MF), hypertrophy (14/25% - - 7 symptomatic - CCI, 8/ 13% MF), Severe: deep vein thrombosis (1/ CCI), severe tendinitis of fascia lata (1/ CCI)	No AE	Reactive synovitis with exudation in ACI group (5/20%)

Conclusion by authors	Both methods have acceptable short term <i>and</i> long term results, no significant difference in histology of tissue and clinical outcome. MF is low cost and minimal-invasive method and therefore preferable.	CCI has superior structural repair compared to MF, tissue was less fibrous and showed elements of higher compressive strength. Trial proves non-inferiority in short term results. Expected clinical benefit may not become manifest until at least 2-3 years after surgery, because cartilage repair may continue to improve.	Both treatments have shown satisfactory clinical outcomes at medium-term follow-up. Authors believe that 2 nd generation ACI is a good and potentially durable option for the treatment of cartilage defects.	The results confirm a better outcome in pts treated with ACI. 2 nd generation ACI avoids hypertrophy or ossification
Comments (study quality: internal/external validity) [41]	The quality of this paper is fair: lack of reporting exact baseline data, high dropout rate, inadequate follow-up procedures and inadequately described side effects.	The quality is excellent: good follow-up, good reporting of side effects/adverse events, drop-out rate is low at 12 months (o), and 50% at 18 months. The authors reported that not all data had been analysed at the time of publishing.	The quality of this study is low: no accurate diagnostic follow-up method and no side effects are reported. No randomization was carried out, marked differences in pre-treatment rates and traumatic cartilage lesions between groups.	The quality of this study is fair: lack of reporting of exclusion criteria, failure rates and only short term follow-up (12 months), differences in rates of pre-treatment and lesion size between treatment groups.
Rating of study quality	fair	good	poor	fair

Abbreviations

AB: Antibodies (here monoclonal)

ACI: Autologous chondrocyte implantation

ADL: Activities of daily living scale

AE: Adverse events

CCI: Characterized chondrocytes implantation

H&E: Haematoxylin and Eosin staining

ICRS: International Cartilage Repair Society

IKDC: International Knee Documentation Committee

KOOS: Knee injury and osteoarthritis Outcome Score

MACI: Matrix associated autologous chondrocytes implantation

MF: Microfracture MP: Mosaicplasty

MRI: Magnetic resonance imaging

n.m.: Not measured

n.r.: Not reported

OAT: Osteochondral autologous transplantation

OCT: Osteochondral cylinder transplantation

RCT: Randomised controlled trial

Table 3.2-2: Comparative Studies – ACI vs. ACI-C vs. MACI, ACI-C vs. ACI-P

Author/Year	Bartlett 2005 [43]	Gooding 2006 [46]
Country	England	England
Study Design N of centres	RCT, MACI (indication) vs. ACI-C 1 centre	RCT, ACI-P vs. ACI-C (indication)
Sponsor/ product used	n.r./academic MACI: Tissell, Baxter, ACI-C: Matricel Herzogenrath	n.r./academic
Patients Age/ sex Number of pre-treatment (surgical interventions) Aetiology of defects	15-50 yr (Ø 33.4: 33.7) male: 62% pre-treated: Ø 2.1: 2.3 trauma (43%), chondromalacia patellae (18%), osteochondritis dissecans (15%)	(Ø 30.52: 30.54) male: 49% pre-treated: Ø 2.09 trauma (43%), chondromalacia patellae (29%), osteochondritis dissecans (18%)
Size of lesion	6.1 (1.0-22): 6.0 (1.5-16) cm ²	4.54(1-12) cm ²
Indication (inclusion)	Osteochondral defects larger than 1 cm ² lo- cated at medial femoral condyle, lateral femoral condyle, patella, trochlea caused by trauma, chondromalacia patellae, osteochon- dritis dissecans,	Isolated full thickness chondral defect (grade 4 Outerbridge), located at medial femoral condyle, patella, lateral femoral condyle, trochlea caused by trauma, chondromalacia patellae, osteochondritis dissecans
Contra-indication (exclusion)	Uncorrected joint instability, malalignment, bone deficiency osteoarthritis, inflammatory joint disease,	Osteoarthritis, multiple defects, limb mala- ignment, cruciate instability
Number of patients (I: C)	91 (47: 44)	68 (33: 35)
Pts lost to follow-up, drop-out	16 (15%)	0 (0%)
Duration of follow-up	12 months	24 months
Outcome measures/ scores used	VAS, Stanmore functional rating score, modi- fied Cincinnati knee score,	Modified Cincinnati knee score, ICRS
Outcome KOOS pre/post (I: C)	n.m.	n.m.
Outcome IKDC subjective pre/post (I: C)	n.m.	n.m.
Outcome IKDC objective pre/post (I: C)	n.m.	n.m.
Outcome pain pre/post (I: C)	n.m.	n.m.
Outcome Lysholm function pre/post (I: C)	n.m.	n.m.
Outcome Meyer pre/post (I: C)	n.m.	n.m.
Outcome Tegner pre/post (I: C)	n.m.	n.m.
Outcome Cincinnati pre/post (I: C)	44.5/64.1: 41.0/59.0 Good/excellent outcome: 72.3%: 59.1%	45/62: 45/67 Good/excellent outcome: 66.4%: 74.3%
Outcome VAS pre/post (I: C)	6.0/4.1: 6.0/4.3	n.m.
Diagnostic controls (MRI, histology, arthroscopy)	Arthroscopy, histology (H&E staining, Safarin O),	Arthroscopy, histology (Safarin O staining only),
Failure	2 MACI (4.3%): 0 (0%) ACI	2 ACI-P (6%)
Side effects/ adverse events	hypertrophy (3 MACI, 4 ACI), manipulation of knee under anaesthesia (3 MACI, 3 ACI), superficial wound infection (1 MACI)	3 (4%) major and 36 (53%) minor complica- tions, ACI-C: Deep vein thrombosis (1), Me- niscal tear shaving (3), lateral popliteal nerve neuropaxia (1), superficial wound infection (1), large plica removed (1), division of adhe- sion and graft hypertrophy (1), septic arthritis (1), Both: Hypertrophy (12/33-ACI-P, 1/35 ACI-C), reflex sympathetic dystrophy (1/1),
Conclusion by authors	Both ACI-C and MACI resulted in significant improvements within one year: functional and pain scores not significantly different, no difference in histological findings after both. Both interventions are associated with fewer graft-related complications and re-operations (compared to ACI-P). Little is known of the long term durability of MACI.	This study suggests that the results are com- parable based on clinical outcome and arthro- scopic assessment at 2 years. However, the most striking feature was the high incidence of graft hypertrophy in the ACI-P group caus- ing considerable morbidity and additional surgery.
Comments (study quality: inter- nal/external validity) [41]	The quality of the study is good: reporting of all relevant data and high quality of histo- logical and functional follow-up.	The quality of the study is fair: in some pas- sages text/tables are not congruent. The complications are reported in detail.
Rating of study quality	good	fair

Table 3.2-3: Comparative studies – ACI vs. mosaicplasty

Author/Year	Bentley 2003 [51]	Dozin 2005 [7]	Horas 2000 [49], 2003 [50]
Country	England	Italy	Germany
Study design Number of centres	RCT, ACI-C vs. MP 1 centre	RCT, ACI-P vs. MP multicenter	non randomised CT, ACI-P vs. OCT 1 centre
Sponsor/ product used	Commercial n.r.	Italian Ministry of Health n.r.	academic Cylinder: DBCS, Merck
Patients age/ sex Number pre-treatment (surgical interventions) Aetiology of defects	16-49 yr (Ø 30.9:31.6) male: 57% pre-treated: 1.5 (0-4) trauma (46%), osteochondritis dissecans (19%), chondromalacia patellae (14%)	16-40 yr (Ø 29.6: 27.9) 1 male: 77.3%: 45.5 pre-treated: none	18-45yr (Ø 31.4: 35.4) male: 40%: 75% pre-treated: 20%: 15% - 1 trauma (100%)
Size of lesion	4.66 (1-12.2) cm ²	1.97±0.43: 1.88±0.45 cm ²	4.4 (3.2-5.8) cm ²
Indication (inclusion)	n.r.	Symptomatic chondral injury of 3-4° (Outerbridge), caused by traumatic, microtraumatic influence, pain, swelling, pseudolocking, femoral condyle, patella, lesions size: up to 2.84 cm ²	Trauma caused only, medial femur condyle, lateral femur condyle
Contra-indication (exclusion)	n.r.	Subchondral bone injury, no previous surgical treatment of interest, overweight, knee joint instability, associated meniscus damage, injured anterior cruciate ligaments, axial misalignment, rheumatoid joint disease, previous or current neoplasty, HIV, HBV, HCV viral infection	Knee joint instability, kissing lesions, axial malalignment, osteochondral tumor
Number of patients (I: C)	100 (58:42)	44 (22:22)	40 (20:20)
Pts lost to follow-up, drop-out	n.r.	21 (30 % spontaneously cured before treatment, 17 % refused surgery)	0 (0%)
Duration of follow-up	19 months (12-26)	36 months	24 months
Outcome measures/ scores used	ICRS, Cincinnati score, Stanmore score	IKDC, Lysholm Knee scaling core	Modified Lysholm, Meyers, Tegner,
Outcome KOOS pre/post (I: C)	n.m.	n.m.	n.m.
Outcome IKDC subjective pre/post (I: C)	n.m.	n.m.	n.m.
Outcome IKDC objective pre/post (I: C)	n.m.	n.r.	n.m.
Outcome pain pre/post (I: C)	n.m.	n.m.	n.m.
Outcome Lysholm function pre/post (I: C)	n.m.	90-100: 45%: 68% 60-90: 22.7%: 9.1%	25-65: 28-72
Outcome Meyer pre/post (I: C)	n.m.	n.m.	9-16: 9-16
Outcome Tegner pre/post (I: C)	n.m.	n.m.	2-5: 2-5
Outcome Cincinnati pre/post (I: C)	88% excellent or good: 69%	n.m.	n.m.
Outcome VAS pre/post (I: C)	n.m.	n.m.	n.m.
Diagnostic controls (MRI, histology, arthroscopy)	Arthroscopy	Arthroscopy, radiology	MRT, arthroscopy, histology (H&E, Mason Goldner, Toluidin-Blau, Immunological: Anticollagen 1, 2, 3, 6, 10, Aggrecan, S-100 protein, monoclonal ABs), electron-microscope,
Failure	n.r.	n.r.	1 (ACI)
Side effects/ adverse events	1 vein thrombosis (1), infection (1)	n.r.	OCT: oedema (1), ACI: hypertrophy (2), mainly fibrous cartilage,

Conclusion by authors	The study has shown, that both MP and ACI give encouraging clinical results after a mean period of 1 year, but MP appears to deteriorate with time. Definite evidence that ACI is valuable for selected patients, the continued use of MP appears to be dubious.	ACI and MP are clinically equivalent and similar in performance. The high percentage of spontaneous improvement (1/3 of the patients) observed after simple debridement calls into question the need for prompt surgical treatment of patients with lesions included in the study.	Both treatments resulted in decrease of symptoms. Improvement provided by ACI (85% of pts.) lagged behind that provided by OCT (85%). Histology shows that the defects treated with ACI were primarily filled with fibrocartilage, whereas OCT retained their hyaline character.
Comments (study quality: internal/external validity) (LBI_manual)[41]	Although this is one of the most cited studies, the quality of the study is poor: lack of reporting of baseline data that allow comparison of groups, esp. lesion sizes, no inclusion/exclusion criteria, no dropout or lost to follow-up rates, side/adverse effects are inadequately described. The randomization process is not described.	The quality of this study is fair: the reasons for the high drop-out rate are reported transparently. No side effects/adverse events or failure rates are reported, one additional outcome (IKDC) was measured, but not reported, histology as diagnostic control is missing. The study seems to have a high external validity and can best be described as "environmental" study. The lesions are small compared to the other studies.	The same trial has been published twice: in German (2000) and in English (2003). The quality of this study is fair: not randomised, has a broad range of physiological follow-up methods, the functional assessment is reported inadequately in 2000 though more precisely in 2003.
Rating of study quality	poor	fair	fair

3.3 Effectiveness

3.3.1 ACI vs. MF

All of the 4 comparative trials on ACI vs. microfracture were (fully or partly) commercially sponsored. Overall the 4 trials included 424 patients between the ages of 16 and 60, of whom about two thirds were male. 80-95% were pre-treated, (fewer in [47]), including patients with symptomatic cartilage lesions with lesion between Ø 2.2 to 5.1 cm² and Outerbridge grades 3-4. The lesions were most often caused by trauma or osteochondritis dissecans. 3 of the 4 trials with follow-up periods of 1 to 5 years concluded that the 2 interventions led to equal or similar clinical outcomes, but that the cost of microfracture was much lower. Only 1 study (quality rating fair because of lack of important information). [48] reported better results for the ACI treated group compared to controls.

Knutsen et al. [44, 45] performed their trial on medium sized lesions, mainly in male patients, in the medial or lateral femoral condyle or trochlea. The 40 patients in each group, ACI-P and MF, showed a similar pre-treatment rate of nearly 1. procedures. The age was higher in the ACI group than in the MF group (33. compared with 31.) and the defect size was larger in ACI group (5. compared with 4. cm²). Not all of the defects were Outerbridge grade 3 or 4. 3 were a grade 2 defect, which were rated by other authors as normal cartilage. The group in which these were observed was not reported.

Even though the trial showed superior ACI results after two years [44, 45], three years later [44, 45] the results were approximately equal: all scoring parameters were significantly raised with both interventions. Histological parameters showed that ACI can lead to the development of hyaline cartilage. It appears that the cartilage can have mixed properties: Fibrous as well as hyaline like tissue was found in the ACI-group.

**4 comparative trials:
2 thirds male,
mostly pre-treated,
grade 3-4 lesions**

**Knutsen et al. 2004,
2007
80 pts
2 & 5 years follow-up**

**only short term
superiority of ACI,**

younger & more active patients had significantly better outcomes in both treatment groups

no difference between interventions after 5 years

The diagram shows outcomes after 2 and 5 years. After 2 years, the failure rate was low in both groups: 2 in the ACI and 1 in the MF group. The mean time to failure was 26 months. There were 9 failures in both groups. All failures had to be retreated using a surgical procedure. In each group one patient was retreated by total knee replacement, and the others had MF, MP or ACI. Younger and more active patients had significantly better outcomes in both treatment groups. The authors concluded that there is a need for improvement in surgical and molecular biological techniques, as well as a need for further long term studies.

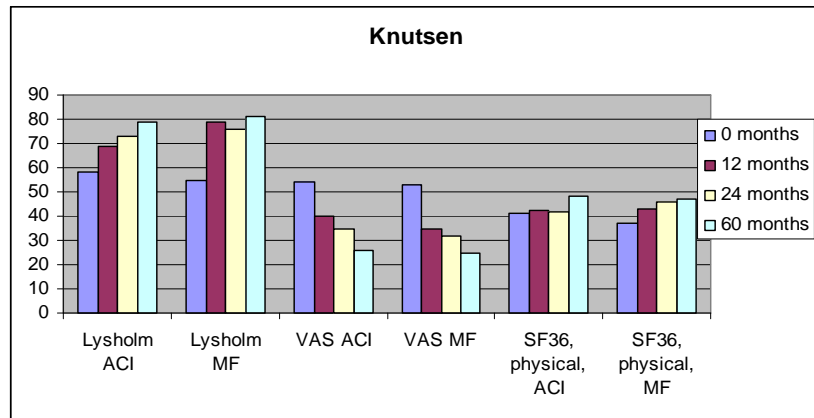


Figure 3.3-1: Knutsen [44, 45]

Saris et al. 2008
118 pts.

limitation of study-
results: 50% of pts lost
to follow-up

superiority of ACI in
structural repair,
but superiority of MF
in QoL

equality in functionality
after 18 m

Saris et al. [42] carried out a trial in 118 patients and had very specific inclusion criteria. Only patients with lesions on the femoral condyle and limited to small to medium sized full thickness lesions were included. The baseline data of the groups were similar in terms of pre-treatment, age, BMI, the body weight and the height. Only the number of pre-treatments differed between the two groups. Unfortunately only data from 59 (50%) of the 118 enrolled patients were available/ presented after the follow-up period of 18 months. Both interventions showed a very low failure rate: 1 for ACI and 2 for MF. The ACI procedure was performed according to the method described by Brittberg and was similar to ACI-P.

Although Safarin O and Collagen 2 staining showed ACI to lead to better structural regeneration of the cartilage tissue - the KOOS subgroup scores increased by 20% after 18 months - there were no differences between MF and ACI. QoL scores increased by about 15% for ACI and by about 21% for MF. These results suggest a superiority of structural repair in ACI characterized by a higher grade of hyaline cartilage areas. This superiority is not confirmed by the functional assessment of the 2 patient groups: the outcomes are equal after 18 months.

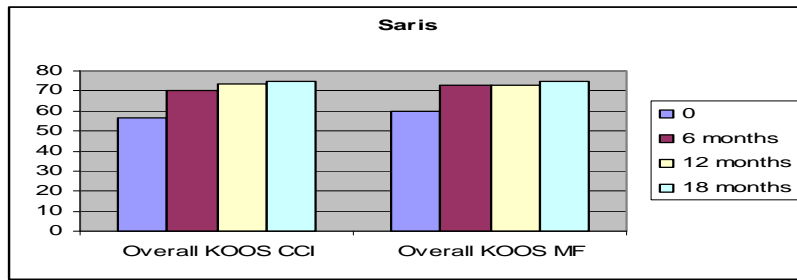


Figure 3.3-2: Saris [42]

In a non-randomised clinical trial 80 active patients with grade 3 or 4 chondral lesions of the femoral condyle or trochlea of 1-5 cm² were treated by Kon et al. [48] using ACI (42) or MF (38). Mean ages were 29 in the MF and 30.6 in the ACI group. The number of males was higher in the ACI-group. The cause of the lesion was significantly different between the groups. In the MF group the main cause was traumatic events, and in the ACI group the main causes were traumatic events and microtraumatic degeneration. There were more pre-treated patients in the ACI-group than in the MF group. The mean lesion sizes were relatively small: 2. (MF) and 2. (ACI) cm². The study population had a high average pre-lesion level of physical activity and the average time to return to sports activities was short.

Kon et al. 2009

80 pts.

“only” 48% pre-treated small lesions highly active pts.

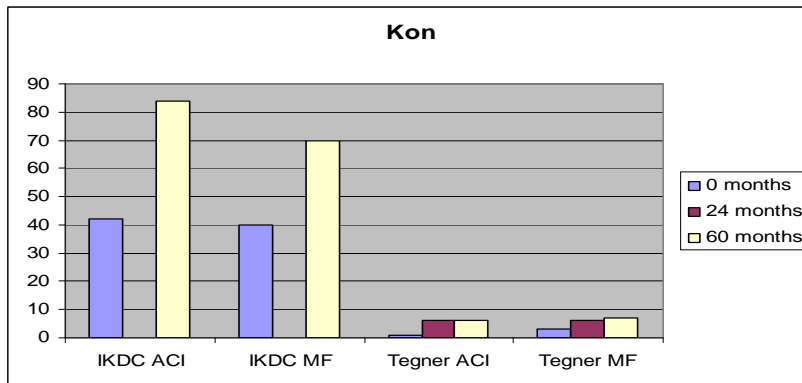


Figure 3.3-3: Kon [47]

Two and five year results were evaluated. At baseline 2.5% of knees in the MF group (IKDC scale) were nearly normal. After 5 years 75% were normal. In the ACI group 15% of knees at baseline were normal. After 5 years follow-up this figure was 90%. The Tegner score (measures the functioning of the knee) also improved, and the sports activity level was maintained. The trial showed that at 5 years follow-up, there was no difference between the outcomes of the two interventions. Based on the results of the IKDC score, better results were observed in the ACI group, but not so according to Tegner. Only 1 failure in each group was reported. The authors conclude that this kind of ACI (Hyalocraft C) is an acceptable treatment option. However, neither an MRI nor a histological analysis has been carried out.

2 & 5 years follow-up:

no difference between interventions, equality

Visna et al. 2004
 50 pts.
 only 12 m follow-up
 superiority of ACI in all
 parameters

Visna et al. [48] carried out an RCT comparing ACI with abrasive technique in 50 patients. The average lesion size in the ACI group was 4.08 cm², in the control group it was 3.36 cm². All patients had full thickness cartilage defects, mostly caused by trauma. ACI shows superiority in all parameters (Lysholm, IKDC, Tegner). The authors conclude that 2nd generation ACI leads to better outcomes than abrasive techniques after one year.

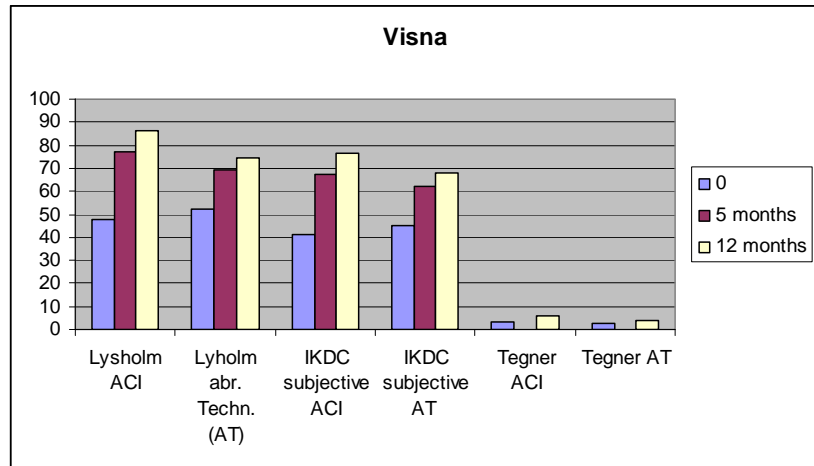


Figure 3.3-4: Visna [48]

3.3.2 ACI vs ACI Methods

2 RCTs

Two RCTs [43, 46] with a total of 159 patients focused on the evaluation of the impact of new (ACI) methods on the clinical effectiveness of ACI. The sponsors of both studies are not reported and are believed to be academic. The quality of these trials was rated as fair [46] and good [43] respectively. The follow-up periods were 12 months [43] and 24 months [46].

Bartlett et al 2005
 91 pts.

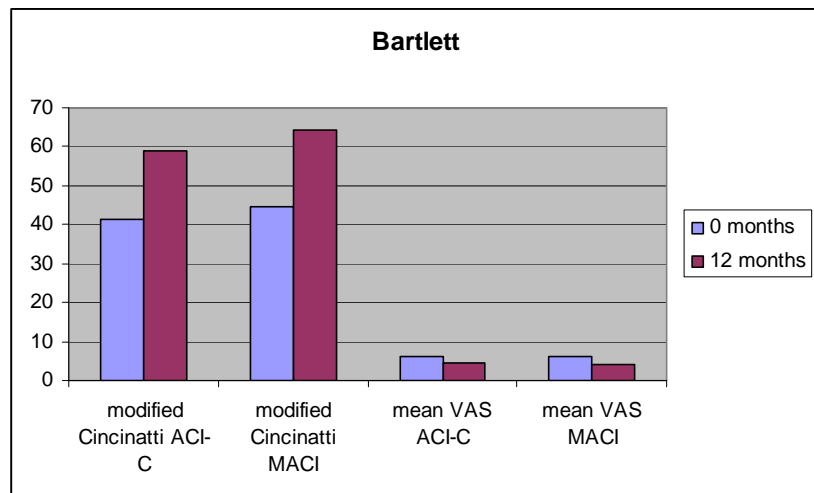


Figure 3.3-5: Bartlett [43]

The study comparing ACI with MACI, performed by Bartlett et al in 2005 [43] is the only controlled clinical trial directly comparing these 2 genera-

tions of ACI. The results suggest similar outcomes for MACI and ACI-C after one year. 107 patients were pooled, and 91 of them were later randomised. The baseline data of the 2 groups were clearly different. The lesions of the patients in the ACI group had been pre-treated more often than those of the MACI group. The mean baseline Cincinnati score was 44.5 for MACI and 41.0 for ACI. The mean lesion size was almost the same in both groups, 6.0 and 6.1 cm².

After one year follow-up the ACI-C group had an increase of 18 points to 59 and the MACI an increase of 20 points to 64.1 in the Cincinnati ranking. The Stanmore score (not shown) showed almost identical improvements in both groups. The VAS score decreased by 2 points in both groups. None of the scoring systems showed significant differences between the two groups. Histological analysis - not performed on every patient - showed that there is only in 42.9% other filling than pure fibrocartilage in the ACI group, and in 36.4% in the MACI group.

The similarities in results might suggest that MACI is preferable to ACI, owing to its more straightforward surgical protocol. However, the study showed that the clinical results were not as good when patients had been pre-treated, and there were a higher percentage of patients with a failed previous therapy in the ACI-C group. Because they compared imbalanced groups, the authors recommend considering MACI as an experimental treatment, and underline the need for further long term trials.

Gooding et al. [46] compared first generation ACI (ACI-P) with second generation ACI (ACI-C). In total 68 patients were randomised into the two groups.

Besides the (equal) mean age of the patients, no other baseline data are reported. The ACI-P group showed - after two years follow-up - an increase in the Cincinnati score from 39.4% good, 33.3% fair and 27.3% poor (baseline), to 30.3% excellent, 36.4% good 21.2% fair and 12.1% poor. The baseline scores in the ACI-C group were with 5% lesser "good", 10% higher "fair" and 4% "lower" poor Cincinnati scores.

Overall, the results are very similar for the two interventions. A one and two year follow-up arthroscopy showed that ACI-C resulted in Outerbridge grades 1 or 2 for 79% of patients one year after and 82% two years after surgery. This is an improvement, but these partly fillings had been reported in both groups as being soft. 80.7% of ACI-P patients had Outerbridge 1 or 2 lesions after one year, and, in a smaller population, only 55% after two years. Histological analyses were carried out in a small group of ACI-C patients after one year: the results showed that mixed cartilage or fibrous cartilage, but not hyaline alone developed. After two years this outcome had changed only little: out of 7 patients only one had been reported to have developed hyaline cartilage. Results in the ACI-P group were similar. After 1 year, only 1 of 8 patients was developing hyaline cartilage, after two years this was the case for 2 of 14 patients. The arthroscopic results showed that there was not a complete healing of the lesion. Gooding et al [46] conclude that the Periosteum patch is not necessarily needed for ACI.

**MACI and ACI:
clinical unimportant
differences,
equal results**

**preference of MACI due
to easier surgical
protocol**

**Gooding et al. in 2008
68 pts.**

**nearly equal results,
decrease in Outerbridge
grading from 3-4 to 1-2**

**same cartilage
consistence**

3.3.3 ACI vs Mosaicplasty (MP)

2 RCTs,
1 non-randomised CT

Trials comparing ACI to mosaicplasty and related techniques were performed on 184 patients by Horas et al. 2000 [49] and 2003 [50], Bentley et al. 2003 [51] and Dozin et al. 2005 [7]. The results differ greatly. The Horas et al. [49, 50] and Dozin et al. [7] trials compared ACI-P methods to MP, while Bentley et al. [51] compared ACI-C to MP. One trial [51] was commercially funded, the two others by academic or public funds.

Bentley et al 2003
100 pts
poor reporting of trial
low evidence in favour
of ACI

The Bentley et al. [51] study enrolled 100 patients and was commercially funded. It was rated as “poor”, due to lack of reporting of baseline data, inclusion/exclusion criteria, and details of adverse effects. Furthermore, they used an accelerated – uncomparable - rehabilitation protocol. The authors conclude that MP can be replaced by ACI-C in selected patients, but adequate evidence for this conclusion is not provided in the publication.

Dozin et al. 2005
44 pts
30% spontaneous
healing prior to surgery

The Dozin et al. [7] study shows a very high drop-out rate, caused by spontaneous healing. After debridement had been performed 6 months prior to surgery, 30% of the patients had healed spontaneously by the time they were due to have their procedures.

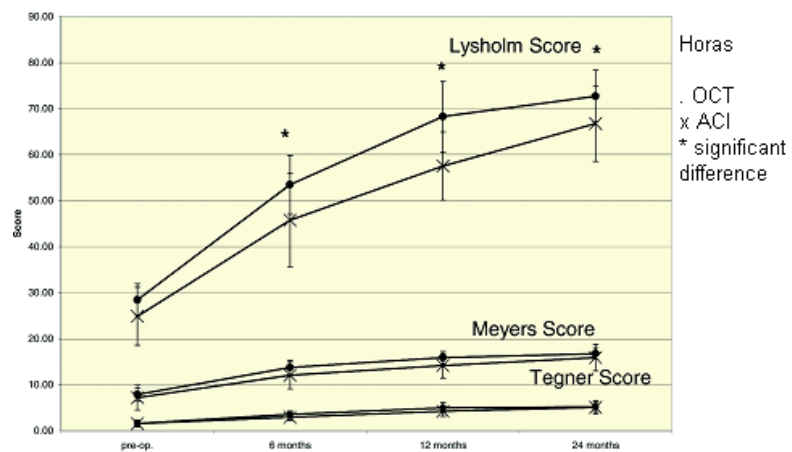


Figure 3.3-6: Horas [49, 50]

Horas et al. 2000, 2003
40 pts.

significant
improvements in both
groups
tendency towards more
favourable results with
OCT

The Horas et al. [49, 50] study enrolled 40 patients who were equally distributed between the ACI-P and the OCT group. The baseline characteristics of the patients were somewhat different in terms of average age (31.4 years in the ACI group vs. 35.4 years in the OCT group), but pre-treatment rates and localisation of the lesions were the same. The size of the lesions was not reported and the 2 years results were presented. The reported scores (Lysholm, Meyer, Tegner) showed very similar and significant improvements after 2 years in both groups. The results tended to favour the OCT intervention. The MRT showed a statistically significant decrease of the signal in the OCT group after 2 years. The ACI group showed differences between the signal of the natural cartilage tissue and the reclaimed material after two years. Arthroscopy of the ACI group proved that regeneration was not taking place. The tissue showed a different elasticity than the normal tissue and had a rough surface. The OCT group showed nearly perfect regeneration. Immunohistochemical analysis showed similar results in both groups. OCT was well integrated, while the ACI reclaimed material was distinguishable from the surrounding tissue. Electron microscopic analysis showed a high migrating

tendency or high cell death rates of the reimplanted chondrocytes in the ACI group, caused by holes of a diameter of one chondrocyte. The collagen structure was of normal appearance in the OCT group, collagen fibers of the ACI group had another 3D structure.

3.4 Results in Systematic Reviews

Systematic reviews were written by Clar et al. [5], Jobanputra et al. [31] Magnussen et al. [52], Ruana-Ravina et al. [28], Vavken et al. [53] and Wasiak et al. [54]. All of them analysed more or less the same clinical trials as described above. Some included/ differences are:

6 systematic reviews

- ✿ trial designs other than RCTs, including observational studies and/or
- ✿ analysis/ assessment of evidence on effectiveness alone or complemented by economic assessment

Table 3.4-1: Conclusions from systematic reviews

	pts randomised	pts not randomised	Conclusion
Jobanputra 2001 [31]	o	2600	Economics:: unclear Long term outcomes are required
Clar 2005 [5]	pts randomised 266	pts not randomised/ observational 101	Conclusion There is insufficient evidence at present to say that ACI is cost-effective, long term outcomes are required.
Magnussen 2008 [52]	pts randomised 421	pts observed o	Conclusion No one technique produces superior clinical results for treatment of full-thickness articular cartilage defects. Available evidence shows limitations
Ruano-Ravina 2005 [28]	pts randomised 220	pts not randomised 464	Conclusion The clinical trials yielded no evidence that ACI was superior to the therapeutic alternatives. Neither in safety nor in effectiveness is a difference.
Wasiak 2006 [54]	pts randomised 266	pts not randomised o	Conclusion Long term outcomes are required
Vavken 2008 [53]	pts randomised 276	pts not randomised 220	Conclusion ACI leads to high quality repair, and therefore should be preferred because of economic superiority

<p>Jobanputra et al. 2001 only case studies: subject to bias</p>	<p>Jobanputra et al. 2001 [37] included 17 studies in their review. At least 2600 patients appear to have been treated with autologous chondrocyte transplantation (ACT). All included studies were case series with a variable length of follow-up. With one exception, all the studies reported improvements in patient status, usually over a follow-up period of less than 2 years. The outcome of ACT surgery was rated as 'good' or 'excellent' by approximately 70% of patients 2 years after treatment. Approximately 16% of patients required further arthroscopic surgical procedures during follow-up, and treatment was judged to have failed in 3–7% of patients. For comparator treatments, the outcome was rated as 'good' or 'excellent' in 10–95% of patients 2 years after treatment.</p>
<p>cost calculations for UK: cost-effectiveness analysis is limited by the poverty of the effectiveness data</p>	<p>For cost-calculations two economic studies, one carried in the USA and the other in Sweden, were included. Neither study compared ACT with other treatments. Using data from these studies and other sources, it was estimated that ACT performed in the UK would cost £4667 or £8167 for cell culture and surgery, depending on which service provider was used for cell culture. Incremental cost over 2 years, when set against comparator treatments, was estimated to be £3771 or £7271 (base case) for cell culture, surgery and rehabilitation.</p>
<p>Clar et al. 2005</p> <p>little difference, equality</p>	<p>The authors conclude, that the reported literature on ACT and comparators is subject to bias because of the inherent weaknesses of case series. In addition, the long-term impact of conventional surgical treatments or no surgical treatment is poorly documented. The cost-effectiveness analysis is similarly limited by the poverty of the effectiveness data on both.</p>
<p>after ACI: it takes 2 years for full-thickness cartilage to be produced</p>	<p>Clar et al. 2005 [5] published a review providing guidance (issued by the National Institute for Health and Clinical Excellence/(NICE) in December 2000. 4 randomised controlled trials were included, as well as observational data from case series. The trials studied a total of 266 patients and the observational studies up to 101 patients. Two studies compared ACI with mosaicplasty, the third compared ACI with microfracture, and the fourth compared MACI with microfracture. Follow-up was 1 year in 1 study, and up to 3 years in the remaining 3 studies. The first trial of ACI versus mosaicplasty found that ACI gave better results than mosaicplasty at 1 year. Overall, 88% had excellent or good results with ACI versus 69% with mosaicplasty. About half of the biopsies after ACI showed hyaline cartilage. The second trial of ACI versus mosaicplasty found little difference in clinical outcomes at 2 years. Disappointingly, biopsies from the ACI group showed fibrocartilage rather than hyaline cartilage. The trial of ACI versus microfracture also found only small differences in outcomes at 2 years. Finally, the trial of MACI versus microfracture contained insufficient long-term results, but showed the feasibility of doing ACI by the MACI technique. The authors conclude that the existing data suggest that after ACI, it takes 2 years for full-thickness cartilage to be produced.</p>
<p>short-term modelling:</p> <p>cost-effective only if ACI would have impact on QoL 70-100% greater than alternatives</p>	<p>Reliable costs per quality-adjusted life-year (QALY) could not be calculated owing to the absence of necessary data. Simple short-term modelling suggests that the quality of life gain from ACI versus microfracture would have to be between 70 and 100% greater over 2 years for it to be more cost-effective within the 20,000-30,000 £ per QALY cost-effectiveness thresholds. However, if the quality of life gains could be maintained for a decade, increments relative to microfracture would only have to be 10-20% greater to justify additional treatment costs within the cost-effectiveness band indi-</p>

cated above. Follow-up from the trials so far has only been up to 2 years, with longer term outcomes being uncertain.

The authors conclude, that there is insufficient evidence at present to say that ACI is cost-effective compared with microfracture or mosaicplasty. Long-term outcomes are required. Economic modelling using some assumptions about long-term outcomes that seem reasonable suggests that ACI would be cost-effective because it is more likely to produce hyaline cartilage, which is more likely to be durable and to prevent osteoarthritis in the longer term (e.g. 20 years). Further research is needed into earlier methods of predicting long-term results. Basic science research is also needed into factors that influence stem cells to become chondrocytes and to produce high-quality cartilage, as it may be possible to have more patients developing hyaline cartilage after microfracture. Study is also needed into cost-effective methods of rehabilitation and the effect of early mobilisation on cartilage growth.

Magnussen et al. 2008 [52] asked whether ACI or osteochondral autograft transfer yields better clinical outcomes compared with one another or with traditional abrasive techniques for treatment of isolated articular cartilage defects and whether lesion size influences this clinical outcome. They identified 5 randomised, controlled trials and 1 prospective comparative trial evaluating these treatment techniques in 421 patients. The operative procedures included ACI, osteochondral autograft transfer, MACI, and microfracture. Minimum follow-up was 1 year (mean, 1.7 years; range, 1-3 years). All studies documented greater than 95% follow-up for clinical outcome measures. No technique consistently had superior results compared with the others. Outcomes for microfracture tended to be worse in larger lesions. All studies reported improvement in clinical outcome measures in all treatment groups when compared with preoperative assessment; however, no control (non-operative) groups were used in any of the studies. A large prospective trial investigating these techniques with the addition of a control group would be the best way to definitively address the clinical questions.

Ruano-Ravina et al. 2005 [28] examined 3 clinical trials and 9 case series. The clinical trials yielded no evidence that ACI was superior to the therapeutic alternatives with which it was compared. In contrast, the case series revealed an improvement in patients. However, as with the clinical trials, the follow-up periods were usually very short. In general few adverse events were observed, indicating that ACI is a safe technique. The authors conclude, that available data afford no evidence that ACI is more effective than other conventional techniques in treating chondral lesions of the knee.

Wasiak et al. [54] is a Cochrane Review from 2006: 4 randomised controlled trials (266 participants) were included. One trial of ACI versus mosaicplasty reported statistically significant results for ACI at one year, but only in a post-hoc subgroup analysis of participants with medial condylar defects; 88% had excellent or good results after ACI compared with 69% after mosaicplasty. A second trial of ACI compared with mosaicplasty found no statistically significant difference in clinical outcomes at two years. There was no statistically significant difference in outcomes at two years in a trial comparing ACI with microfracture. In addition, 1 trial of matrix-guided ACI compared with microfracture did not contain enough long-term results to reach definitive conclusions. The authors conclude that the use of ACI and other chondral resurfacing techniques is becoming increasingly widespread, but that there is at present no evidence of significant difference between ACI

long-term outcomes are required

Magnussen et al. 2008

no technique consistently had superior results

Ruano-Ravina et al. 2005: spanisches HTA

no evidence for superiority

Wasiak et al: Cochrane Review 2006

no difference

Vavken et al. 2008
short-term equality
possibility of better
long term results

and other interventions. Additional good quality randomised controlled trials with long-term functional out-comes are required.

Vavken et al. 2008 [53] reviewed 6 randomised controlled studies on the effectiveness of ACT compared with microfracture or mosaicplasty. 4 studies report no or only insignificant differences - one of them recently presented 5-year results - whereas 2 studies observed better results with ACT. Long-term results are good throughout, but the high quality of the regenerative tissue is a clear advantage of ACT. Cost-effectiveness models support ACT for the longevity of its results and thus relatively lower costs in the long-term. The authors conclude, that ACT is an expensive and complex procedure and that in direct comparison with alternative treatments ACT produces results at least as good in the short-term, and most likely better in the long-term due to the high quality repair tissue. Thus higher initial costs are compensated for with time, so the expectations.

To summarize, the systematic reviews include, to a large extent, the same trials as have been described in this review. Most of them state the short-term equality (for a much higher prize) and the need for further long term trials.

3.5 Safety & Morbidity

Table 3.5-1 Safety and Morbidity

<p>Revisions: additional surgical procedures</p>	<p>Repetition of primary intervention Trimming High tibial osteotomy Debridment</p>
<p>Adverse events</p>	<p>Psoriatic arthritis Graft hypertrophy Arthrofibrosis Deep vein thrombosis Severe tendinitis of fascia lata Arthralgia Joint swelling Joint crepitation Reactive synovitis with exudation Superficial wound infection Meniscal tear overgrowth Lateral popliteal nerve neuropraxia Large plica removed Septic arthritis Reflex sympathetic dystrophy Edema</p>

The most frequently reported side effects for microfracture, mosaicplasty, ACI and MACI are joint swelling, joint crepitation, arthralgia and graft hypertrophy. Additionally the need of surgical revision is reported commonly for ACI, MACI and microfracture.

surgical revision and side effects

Due to inconsistent reporting aggregated statements are barely possible and may likely be biased. However, from the included studies there can be summarised a tendency for ACI and MACI to lead to the highest rates of surgical revisions. Joint swelling and arthralgia is common in microfracture and ACI. Highest rates of graft hypertrophy and crepitation are found in ACI. Rare side effects include deep vein thrombosis, edema, superficial wound infection, reactive synovitis as well as psoriatic arthritis, arthrofibrosis, tendinitis, meniscal tear overgrowth, nerve neuropraxia, septic arthritis and reflex sympathetic dystrophy

4 Discussion

In this review only comparative clinical trials (7 randomised, 2 non-randomised) involving 566 patients were included. All of them were carried out by different trial groups, which used different products and procedures. Nevertheless the clinical results are consistent in their suggestion that ACI and (M)ACI lead to similar short term (1-2 years follow-up) and medium term (2-5 years follow-up) results compared to microfracture and mosaicplasty. These findings support the results of the 6 systematic reviews (Cochrane Report, HTA-reports) written 2001 to 2008.

Only a few trials suggested that ACI patient outcomes were better than control group outcomes. However, in all these studies, baseline data varied significantly between the groups. The results of trials with positive outcomes comparing ACI techniques to conventional techniques were not sufficient to lead to statistical significant differences. The majority of trials are ignoring the MRI method. Differences in patients, activity, age, but as well BMI, were comparable between those trials. Unfortunately, most trials had a high drop out rate. Even after 20 years of ACI-trials long-term data are still missing.

Furthermore, both histological and immunohistochemical methods showed the development of mixed cartilage, consisting of both fibrous tissue and hyaline tissue, to be the best ACI outcome, but none of those trials had reported the percentage of this ratio or its development. No trial used medium density gene expression profiling for analysis.

Due to inconsistent reporting of adverse events aggregated statements on the safety of ACI-techniques are barely possible. Nevertheless microfracture and mosaicplasty seem to have both slightly lower rates of adverse events than the ACI technique. Hypertrophy of cartilage seem to be an important safety issue. The need for quality assurance standards and the relevance for the impact on cultivation of the cells is reasonable. Development of MRI and molecular biological methods, can lead to a better understanding of cell behaviour, in particular migration abilities, cells re-differentiation and cell division properties, which is hardly asked in those trials, but frequently their were observable malfunctions of these parameters.

In fact there is only one clinical trial [50] using electron microscopy as parameter. This trial is reporting differences in between the ACI treated and the OCT treated cartilage on cells surface. These patterns have to be analysed as they must be the result of a change in transcriptional, and reasoned by that in a translational and modificational change of proteins' state. The detectable change in mRNA expression can be analysed by use of microarray. There is no doubt that these observation can be performed additionally to an histology, caused by the fact that an mRNA analysis is needing only small amounts of tissue, and standard samples, for comparison, could be taken while the collection of cells for cultivation is taking place. Basically, controls are done while cultivation. So the development, analogue to the metabolism products of pharmaceuticals, of these cells should be shown.

Economic aspects of ACI have been discussed in most of the systematic reviews. All but one review conclude that long term results are needed and that there is no trial evidence that the higher costs of the ACI technique are justified.

consistent results in several comparative trials and international systematic reviews:

equality of ACI

different patient populations, study designs: difficult to compare

high drop-out rates

histological & immunohistochemical follow-up: only mixed cartilage

safety

high standards of quality assurance required

controls of cells surface: change of protein states

much higher costs

impact of BMI & activity at baseline important	The influence of baseline BMI and physical activity level of patients was shown in all of the studies. Regardless of the type of treatment or the age of the patient, it was shown that the higher the Tegner score or the lower the BMI at baseline, the better are the outcomes.
localisation of lesion not important for outcome	There were no differences between the localisations or aetiology of the treated defects. All treatments seem to be similar, or differences in outcome were not been reported, apart from Bentley et al. 2003, who reported a better development of the medial condyle treatment and this result is not underlined by their baseline data.
in terms of outcome no obvious difference between ACI generations	ACI vs. (M)ACI outcomes also seem to be very similar. There were fewer cases of hypertrophy after ACI-C than ACI-P treatment, but the functional scoring systems seem to indicate that ACI-P regeneration properties are higher than in ACI-C. Technical development is slower, and leads to a poorer outcome than expected. There is no evidence that newer generations of technologies are associated with significant outcomes improvements. The main differences were observed between ACI-P and arthroscopic ACI-C, which is far less expensive, and easier to perform.
(M)ACI easier to perform	In conclusion, it must be said that ACI methods remain experimental techniques.

5 Conclusion

short term equality to much higher costs	There is no evidence that ACI or MACI leads to better outcomes than any of the alternative treatments. ACI is not superior; at best equal, at much higher cost. The short term non-inferiority in highly selected active patients is proven. Long-term data are lacking. ACI methods must be considered as experimental techniques.
ACI: experimental technique	Furthermore, there is a need for safety trials that focus on cell migration, or absence, the development of re-implanted cells, and the genexpression profiles, by use of microarray technology. The expression of genes, responsible for surface structure, the proliferation pathways, apoptotic pathways and proteins regulating extracellular matrix embedding, should be considered as important targets of analysis. The impact of changes in genexpression, and protein state, which still are the base of every medical intervention, have to be handled with care. There is a doubtless difference between implanted chondrocytes and natural chondrocytes. This, by the unknown source of cell-behaviour change, and the absence of long-term data of ACI, cannot be ignored, and have to be seen as a risk.
need for safety trials: difference between implanted & natural chondrocytes	
risk-assessment necessary	

6 Literature

- [1] Brittberg M, Brittberg M. Autologous chondrocyte transplantation. *Clinical Orthopaedics & Related Research*. 1999 Oct(367 Suppl):S147-55.
- [2] Vanlauwe J, Almqvist F, Bellemans J, et al. Repair of symptomatic cartilage lesions of the knee: the place of autologous chondrocyte implantation. *Acta Orthopaedica Belgica*. 2007 Apr;73(2):145-58.
- [3] Messner K, Maletius W. The long-term prognosis for severe damage to weight-bearing cartilage in the knee: A 14-year clinical and radiographic follow-up in 28 young athletes. *Acta Orthopaedica Scandinavica*. 1996;67(2):165-8.
- [4] Prakash D, Learmonth D. Natural progression of osteo-chondral defect in the femoral condyle. *Knee*. 2002;9(1):7-10.
- [5] Clar C, Cummins E, McIntyre L, et al. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)*. 2005 1-82, 2005 Dec;9(47):iii-iv.
- [6] Lohff ARB. *Gender Medizin*: Springer Verlag 2008.
- [7] Dozin B, Malpeli M, Cancedda R, et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomised clinical trial. *Clinical Journal of Sport Medicine*. 2005 Jul;15(4):220-6.
- [8] Domayer SE, Welsch GH, Dorotka R, et al. MRI monitoring of cartilage repair in the knee: a review. *Seminars in Musculoskeletal Radiology*. 2008 Dec;12(4):302-17.
- [9] Bhosale AM, Richardson JB. Articular cartilage: structure, injuries and review of management. *British Medical Bulletin*. 2008 Sep;87(1):77-95.
- [10] Matsusue Y, Yamamuro T, Hama H. Arthroscopic multiple osteochondral transplantation to the chondral defect in the knee associated with anterior cruciate ligament disruption. *Arthroscopy*. 1993;9(3):318-21.
- [11] Behrens P, Bosch U, Bruns J, et al. [Indications and implementation of recommendations of the working group "Tissue Regeneration and Tissue Substitutes" for autologous chondrocyte transplantation (ACT)]. *Zeitschrift für Orthopädie und Ihre Grenzgebiete*. 2004 Sep-Oct;142(5):529-39.
- [12] Marlovits S, Zeller P, Singer P, et al. Cartilage repair: generations of autologous chondrocyte transplantation. *European Journal of Radiology*. 2006 Jan;57(1):24-31.
- [13] Minas T, Bryant T, Minas T, Bryant T. The role of autologous chondrocyte implantation in the patellofemoral joint. *Clinical Orthopaedics & Related Research*. 2005 Jul(436):30-9.

- [14] Minas T, Chiu R, Minas T, Chiu R. Autologous chondrocyte implantation.[see comment]. *American Journal of Knee Surgery*. 2000;13(1):41-50.
- [15] Jubel A, Andermahr J, Schiffer G, et al. Transplantation of de novo scaffold-free cartilage implants into sheep knee chondral defects. *American Journal of Sports Medicine*. 2008 Aug;36(8):1555-64.
- [16] Potter HG, Chong le R, Sneag DB, et al. Magnetic resonance imaging of cartilage repair. *Sports Medicine & Arthroscopy Review*. 2008 Dec;16(4):236-45.
- [17] Trattinig S, Domayer S, Welsch GW, et al. MR imaging of cartilage and its repair in the knee - a review. *European Radiology*. 2009 Jul;19(7):1582-94.
- [18] Roberts S, McCall IW, Darby AJ, et al. Autologous chondrocyte implantation for cartilage repair: monitoring its success by magnetic resonance imaging and histology. *Arthritis Research & Therapy*. 2003;5(1):R60-73.
- [19] Briggs KK, Lysholm J, Tegner Y, et al. The reliability, validity, and responsiveness of the Lysholm score and Tegner activity scale for anterior cruciate ligament injuries of the knee: 25 years later. *The American journal of sports medicine*. 2009;37(5):890-7.
- [20] Smith HJ, Richardson JB, Tennant A. Modification and validation of the Lysholm Knee Scale to assess articular cartilage damage. *Osteoarthritis and Cartilage*. 2009 Jan;17(1):53-8.
- [21] Bekkers JEJ, de Windt TS, Raijmakers NJH, et al. Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. *Osteoarthritis and Cartilage*.
- [22] Bartlett W, Gooding CR, Carrington RWJ, et al. The role of the Short Form 36 Health Survey in autologous chondrocyte implantation. *Knee*. 2005;12(4):281-5.
- [23] Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. *Emergency Medicine Journal*. 2001;18(3):205-7.
- [24] www.sportsmed.org/tabs/research/downloads/IKDC_deutsch.pdf. Formblatt 2000 IKDC.
- [25] Rosenberger RE, Gomoll AH, Bryant T, Minas T. Repair of large chondral defects of the knee with autologous chondrocyte implantation in patients 45 years or older. *American Journal of Sports Medicine*. 2008;36(12):2336-44.
- [26] Peterson L, Minas T, Brittberg M, Lindahl A. Treatment of osteochondritis dissecans of the knee with autologous chondrocyte transplantation: Results at two to ten years. *Journal of Bone and Joint Surgery - Series A*. 2003;85(SUPPL. 1):17-24.
- [27] Haute Autorite de Sante/HAS FNAfH. Autologous chondrocyte implantation in the knee joint. Haute Autorite de Sante (French National Authority for Health) (HAS). 2005(54).

- [28] Ruano-Ravina A, Jato Diaz M, Ruano-Ravina A, Jato Diaz M. Autologous chondrocyte implantation: a systematic review. *Osteoarthritis & Cartilage*. 2006 Jan;14(1):47-51.
- [29] Ruano-Ravina A P-CS. Guided use of autologous chondrocyte implant: a five-year follow-up. *Galician Agency for Health Technology Assessment (AVALIA-T)* 2009. 2009.
- [30] Autologous chondrocyte implantation. An updated systematic review and tutelage use extension. *Galician Agency for Health Technology Assessment AVALIA-T*. 2008.
- [31] Jobanputra P, Parry D, Fry-Smith A, et al. Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review. *Health Technology Assessment (Winchester, England)*. 2001;5(11):1-57.
- [32] Excellence NfC. The use of autologous chondrocyte implantation for the treatment of cartilage defects in knee joints. *Institute for Clinical Excellence (NICE)* 2005;28.
- [33] Scotland NQi. The use of autologous chondrocyte implantation for the treatment of cartilage defects in knee joints (review). . *NHS Quality Improvement Scotland (NHS QIS)* 2005.
- [34] Association BCBS. Autologous chondrocyte transplantation of the knee. *Chicago IL: Blue Cross Blue Shield Association (BCBS)* 2003;79.
- [35] Meeting. Autologous chondrocyte implantation for knee cartilage defects. *ECRI*. 2004;35.
- [36] Care SCoTAiH. Autologous chondrocyte transplantation in treating cartilage damage in the knee - early assessment briefs (ALERT). . *Swedish Council on Technology Assessment in Health Care SBU*. 2000.
- [37] Bundesvereinigung/KBV K. Autologe Chondrozytenimplantation. 2000.
- [38] Autologe matrixinduzierte Chondrogenese (AMIC), . *Neue Untersuchungs- und Behandlungsmethoden IneEK-Liste*. 2009;45.
- [39] GB-A GB. Matrixassoziierte autologe Chondrozyten-implantation am Kniegelenk. 2009.
- [40] Peterson L, Minas T, Brittberg M, et al. Two-to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clinical Orthopaedics and Related Research*. 2000(374):212-34.
- [41] Gartlehner. *Manual Abläufe und Methoden*. 2008.
- [42] Saris DB, Vanlauwe J, Victor J, et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomised controlled trial versus microfracture.[see comment]. *American Journal of Sports Medicine*. 2008 Feb;36(2):235-46.
- [43] Bartlett W, Skinner JA, Gooding CR, et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee. A prospective, random-

- ised study. *Journal of Bone and Joint Surgery - Series B*. 2005;87(5):640-5.
- [44] Knutsen G, Isaksen V, Johansen O, et al. Autologous Chondrocyte Implantation Compared with Microfracture in the Knee: A Randomised Trial. *Journal of Bone and Joint Surgery - Series A*. 2004;86(3):455-64.
- [45] Knutsen G, Drogset JO, Engebretsen L, et al. A randomised trial comparing autologous chondrocyte implantation with microfracture: Findings at five years. *Journal of Bone and Joint Surgery - Series A*. 2007;89(10):2105-12.
- [46] Gooding CR, Bartlett W, Bentley G, et al. 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 Jun;13(3):203-10.
- [47] Kon E, Gobbi A, Filardo G, et al. Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the knee: Prospective nonrandomised study at 5 years. *American Journal of Sports Medicine*. 2009;37(1):33-41.
- [48] Visna P PL, Cizmár I, Hart R, Hoch J. Treatment of deep cartilage defects of the knee using autologous chondrograft transplantation and by abrasive techniques - A randomised controlled study *Acta Chir Belg* 2004 Nov-Dec;104(6):709-14. 2004.
- [49] Horas U SR, Pelinkovic D, Herr G, Aigner T. Osteochondral transplantation versus autogenous chondrocyte transplantation. A prospective comparative clinical study. *Chirurg*. 2000;2000 Sep;71(9):1090-7.
- [50] Horas U, Pelinkovic D, Herr G, et al. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. A prospective, comparative trial. *Journal of Bone and Joint Surgery - Series A*. 2003;85(2):185-92.
- [51] Bentley G, Biant LC, Carrington RWJ, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *Journal of Bone and Joint Surgery - Series B*. 2003;85(2):223-30.
- [52] Magnussen RA, Dunn WR, Carey JL, Spindler KP. Treatment of focal articular cartilage defects in the knee: a systematic review. *Clinical Orthopaedics and Related Research*. 2008;466(4):952-62.
- [53] Vavken P, Gruber M, Dorotka R, et al. [Tissue engineering in orthopaedic surgery--clinical effectiveness and cost effectiveness of autologous chondrocyte transplantation]. *Zeitschrift fur Orthopadie & Unfallchirurgie*. 2008 Jan-Feb;146(1):26-30.
- [54] Wasiak J, Clar C, Villanueva E. Autologous cartilage implantation for full thickness articular cartilage defects of the knee. *Cochrane database of systematic reviews (Online)*. 2006;3.