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# Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee (Review)

Vasiliadis HS, Wasiak J

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Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee.
*Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD003323.
DOI: 10.1002/14651858.CD003323.pub3.

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[Intervention Review]

# Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee

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**Editorial group:** Cochrane Bone, Joint and Muscle Trauma Group.
**Publication status and date:** New search for studies and content updated (no change to conclusions), published in Issue 7, 2011.

**Citation:** Vasiliadis HS, Wasiak J. Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee. *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD003323. DOI: 10.1002/14651858.CD003323.pub3.

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## ABSTRACT

### Background

Treatments for managing articular cartilage defects of the knee, including drilling and abrasion arthroplasty, are not always effective. When they are, long-term benefits may not be maintained and osteoarthritis may develop. An alternative is autologous chondrocyte implantation (ACI), the surgical implantation of healthy cartilage cells into the damaged areas.

### Objectives

To determine the efficacy and safety of ACI in people with full thickness articular cartilage defects of the knee.

### Search methods

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (14 January 2011), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2010, Issue 4), MEDLINE (1948 to January Week 1 2011), EMBASE (1980 to Week 1 2011), SPORTDiscus (1985 to 14 January 2011), the WHO International Clinical Trials Registry Platform (26 January 2011), and Current Controlled Trials (26 January 2011).

### Selection criteria

Randomised and quasi-randomised trials comparing ACI with any other type of treatment (including no treatment or placebo) for symptomatic cartilage defects of the medial or lateral femoral condyle, femoral trochlea or patella.

### Data collection and analysis

Review authors selected studies for inclusion independently. We assessed risk of bias based on adequacy of the randomisation and allocation concealment process, potential for selection bias after allocation and level of masking. We did not pool data due to clinical and methodological heterogeneity.

### Main results

Six heterogeneous trials were identified with 442 participants. Methodological flaws of the included trials included incomplete follow-up and inadequate reporting of outcomes. Three trials compared ACI versus mosaicplasty. One reported statistically significant results in favour of ACI at one year in the numbers of people with 'good' or 'excellent' functional results. Conversely, another trial found significant improvement for the mosaicplasty group when assessed using one functional scoring system at two years, but no statistically significant


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differences based on two other scoring systems. A third trial found no difference between ACI and mosaicplasty, 10 months on average after the surgery.

There was no statistically significant difference in functional outcomes at two years in a single trial comparing ACI with microfracture nor in the functional results at 18 months of a single trial comparing characterised chondrocyte implantation versus microfracture. However, the results at 36 months for this trial seemed to indicate better functional results for characterised chondrocyte implantation compared with those for microfracture. The sixth trial comparing matrix-guided ACI versus microfracture found significantly better results for functional outcomes at two year follow-up in the MACI group.

**Authors' conclusions**

There is insufficient evidence to draw conclusions on the use of ACI for treating full thickness articular cartilage defects in the knee. Further good quality randomised controlled trials with long-term functional outcomes are required.

## PLAIN LANGUAGE SUMMARY

**Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee**

A layer of cartilage covering the knee joint surfaces acts to protect the joint and reduce friction. Damage to the cartilage (articular surface) can decrease mobility of the joint and cause pain on movement. Continuing deterioration of the surface may lead to osteoarthritis. Treatments for damaged cartilage include relieving symptoms, surgically cleaning up the joint, or surgically re-establishing the cartilage layer. The latter is done using marrow stimulation techniques (such as microfracture), mosaicplasty (also known as osteochondral cylinder transplantation), and more recently with implantation of healthy cartilage cells (chondrocytes). In the technique of autologous chondrocyte implantation (ACI), a small piece of cartilage is retrieved from the knee joint. This piece is brought to a laboratory where it is digested to free the chondrocyte cells; these cells are subsequently cultured in a culture media in order to expand the numbers of cells. Then, with a second surgery, the cells are placed into the joint defect in an effort to produce a tissue that substitutes the normal cartilage.

This review includes six small randomised controlled trials that compared ACI with either mosaicplasty or microfracture. Although there are some promising results for ACI compared with microfracture from one trial, the evidence from two other trials testing the same comparison did not confirm these. None of the other three trials testing different comparisons provided conclusive evidence in favour of ACI, although the longer-term results suggest that the results for some types of ACI may improve over time. The review identified several ongoing trials that should help to provide evidence to inform on the use of ACI in the future. Meanwhile, there is insufficient evidence to draw conclusions on the use of ACI.


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## BACKGROUND

### Description of the condition

Cartilage provides coverage for bones in their joint surfaces. Its role is essential in decreasing the friction between the joining bones and it also decreases the mechanical load effect on the covered bone. Loss of cartilage and exposure of the subchondral bone may produce crepitation and pain during the joint movements, and repeated joint effusions (Buckwalter 1998).

Cartilage consists of cells (chondrocytes), water and extracellular matrix of collagen (mainly type II), proteoglycans and noncollagenous proteins. In mature articular cartilage, chondrocytes no longer divide and receive their nutrition mainly through diffusion from the synovial fluid. This limits their intrinsic capacity for repair and, thus, cartilage lesions are very difficult to heal. If left untreated lesions are more likely to deteriorate, subsequently exposing the subchondral bone or forming fibrous tissue. The latter, even when successfully covering underlying bone, does not provide adequate mechanical and functional support and is subject to wear over time. Thus, no normal hyaline cartilage is formed and, furthermore, there is usually no improvement of the person's symptoms in the long term.

Isolated lesions to cartilage should be differentiated from osteoarthritis, which refers to diffuse damage to the articular surface, is more common in older people and is generally considered to be irreversible. Non-osteoarthritis cartilage lesions are most often found in younger people and are more subject to various treatment alternatives aiming to cartilage repair or reconstruction (Browne 2000).

### Description of the intervention

There are no uniform approaches to managing defects to cartilage. Surgical treatment options, intending primarily to achieve symptomatic relief with the least amount of invasive intervention (NICE 2005), are usually divided into marrow-stimulating (reparative) and reconstructive techniques. Marrow-stimulating techniques such as subchondral drilling, abrasion arthroplasty, spongialisation or microfractures allow bone marrow cells derived from the subchondral bone to migrate into the cartilage lesion area (Ficat 1979; Johnson 2001; Steadman 2003). The aim of these techniques is to replenish cartilage through the recruitment of progenitor cells as potential cartilage precursors, allowing the development into chondrogenic cells and, finally, cartilage.

Reconstructive techniques use autografts, allografts or synthetic material for restoring the lesion area. The use of autogenous periosteal or perichondrial grafts has been proposed in the past but is not extensively used. Allografts, synthetic polymers or ceramics are often used, usually in forms of osteochondral cylindrical plugs to reconstruct or replace the lesion area (Ghazavi 1997). Mosaicplasty (osteochondral cylinder transplantation) uses small cylindrical autografts harvested from less weight-bearing areas of the femoral condyle articular surface (e.g. intercondylar notch) and placed in the cartilage defect (Hangody 1998).

Marrow-stimulating techniques have offered an easy-to-perform treatment option for full thickness cartilage lesions of the knee. However, according to several studies, repair tissue is mainly fibrotic and lacks the biomechanical and viscoelastic characteristics of normal hyaline cartilage. Thus, clinical results appear to be inferior, unpredictable and not durable compared to other techniques (Minas 1998). In addition, reconstructive techniques also have not managed to provide impressive clinical results. Mosaicplasty, the most common technique, is considered technically difficult procedure not easily performed by the average surgeon. The uses of synthetic grafts have not been extensively studied and only a few cohort studies have been published.

Autologous chondrocyte implantation (ACI) was introduced in Sweden in 1987, being the first biological approach to the management of cartilage lesions (Brittberg 1994). ACI of the knee is a two-stage procedure. The initial stage involves arthroscopy, where the knee is examined, the lesion is evaluated and small pieces of healthy cartilage are harvested from a less weight-bearing area (usually the femoral notch or the medial or lateral rim of trochlea). Individual chondrocytes are isolated in vitro by collagenase digestion, cultured in media containing patient's serum, and, following a period of cellular division, chondrocytes are retrieved for re-implantation.

Re-implantation is the second stage of the process. A parapatellar arthrotomy is undertaken and the defect is debrided to the subchondral bone. Through a second incision, a periosteal patch is harvested from the proximal medial tibia and sutured to the defect rim. Fibrin glue or sealant is applied to the peripheral border of the patch to create a watertight seal. Then, the harvested chondrocytes are injected beneath the periosteal patch (Brittberg 2008).

Surgical techniques and technologies have undergone substantial development since the procedure was introduced. For instance, the above-described operative techniques are considered conventional, first generation approaches. 'Second generation' ACI techniques use manufactured cell carriers such as *MACI* (Verigen AG, Leverkusen, Germany) aiming to provide and stabilise the cells to the defect area (Bartlett 2005). Moreover, other materials like collagen membranes may be used in place of periosteum (type I/III collagen membrane (*ChondroGide*; Geistlich, Wollhausen, Switzerland or *Restore*; De Puy, Warzaw, Indiana, USA) (Gooding 2006; Steinwachs 2007). These materials aim to decrease operation time, limit surgical trauma and avoid complications attributed to the use of periosteum (e.g. graft overgrowth).

'Third generation' ACI uses three-dimensional (3D) matrices such as hyaluronic acid (*Hyalograft-C*; Fidia, Italy) as scaffolds (Kon 2009; Marcacci 2005). Chondrocytes are cultured in these scaffolds in a 3D culture before implanting in the lesion area. The process of implantation (i.e. the second stage of the procedure) in second and third generation techniques can also be performed arthroscopically or with a small incision (Brittberg 2008).

A new technique called 'Characterized Chondocyte Implantation' (CCI) (ChondroCelect, TiGenix NV, Haasrode, Belgium) aims to improve the results of articular regeneration with chondrocyte cell therapy through the use of a selected cell population. Characterised chondrocytes are an expanded population of chondrocytes that expresses a marker profile (a gene score) potentially predictive of the capacity to form hyaline-like cartilage in vivo in a consistent and reproducible manner. The surgical technique is performed as the conventional ACI, however with the use of selected-characterised chondrocytes (Dell'Accio 2003). With the CCI technique, there is a selection of patients with high potential for success; thus, there is a possibility that the


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cells will not be implanted due to a low potential of the patient's chondrocytes to give satisfactory clinical results (shown as a low gene score).

### How the intervention might work

A number of studies have suggested the effectiveness of ACI for cartilage defects of the knee (Peterson 2010; Vasiliadis 2010a; Vasiliadis 2010c; Zaslav 2009). Cohort studies have also shown a durability of good and excellent results in terms of clinical evaluation or histological assessment of biopsies, even up to 11 years after the implantation (Brun 2008; Peterson 2002). Supporters of this technique highlight that it is the only biological approach to chondral defects, suggesting the efficiency gained by using chondrocytes for the restoration of cartilage. However, ACI has its limitations. It demands a steeper learning curve, at least compared with marrow-stimulating techniques. It is also an expensive procedure with a considerable rate of complications (Wood 2006).

### Why it is important to do this review

Cartilage lesions are common in the general population and are more often anticipated in young and physically active people. Curl and colleagues report an incidence of chondral lesions in 63% of the 31,516 performed arthroscopies, with an average of 2.7 lesions per knee (Curl 1997). In 1000 consecutive arthroscopies examined by Hjelle and colleagues, chondral or osteochondral lesions of any type were found in 61% and focal defects were found in 19% (Hjelle 2002). ACI is a relatively new technique with promising results. However, the clinical benefits and potential harms remain unclear.

## OBJECTIVES

The objective of this review was to assess the effectiveness and safety of ACI in people who require repair of clinically significant, symptomatic defects of the medial or lateral femoral condyle, femoral trochlea and patella caused by acute or repetitive trauma to the knee joint or osteochondritis dissecans.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We considered any randomised or quasi-randomised (for example, allocation by hospital record number or date of birth) controlled trials with the comparisons described in the Types of interventions.

#### Types of participants

We were interested in studies enrolling people between 15 and 55 years of age with symptomatic isolated cartilage defects (surface area of 1 $cm^2$ to 15 $cm^2$) of the medial or lateral femoral condyle, femoral trochlea or patella. In these studies, the joint should be free from disease states such as rheumatoid arthritis or osteoarthritis, as determined by radiographic evidence such as joint space narrowing, osteophyte formation, subchondral bony sclerosis or cyst formation.

#### Types of interventions

Interventions comparing ACI with placebo, no treatment or another intervention such as mosaicplasty, periosteal grafting and tibial/femoral osteotomies. We did not include studies comparing ACI with modified versions of ACI such as porcine-derived type I/type III collagen as a cover (ACI-C) or matrix-guided autologous chondrocyte implantation (MACI).

#### Types of outcome measures

We chose six outcome measures as being most representative of the clinically important measures of effectiveness. They included the following:

- knee function scoring systems such as the Lysholm score, the Tegner score, the Cincinnati Knee Scale (CKS) and the Knee Society Score (KSS);
- general function or mobility scoring systems such as the Western Ontario McMaster Osteoarthritis Scale (WOMAC);
- quality of life scoring systems such as Short Form-36 (SF-36);
- symptomatology such as pain and swelling;
- hyaline cartilage development as verified by second look arthroscopy or magnetic resonance imaging (MRI); and
- adverse events.

### Search methods for identification of studies

#### Electronic searches

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (14 January 2011), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2010, Issue 4), MEDLINE (1948 to January Week 1 2011), EMBASE (1980 to Week 1 2011), SPORTDiscus (1985 to14 January 2011), the WHO International Clinical Trials Registry Platform (26 January 2011), and Current Controlled Trials (26 January 2011). We applied no language restrictions.

In MEDLINE, the subject specific search strategy was combined with the Cochrane highly sensitive search strategy for identifying reports of RCTs (Higgins 2006). The EMBASE subject specific search strategy was combined with the Scottish Intercollegiate Guidelines Network (SIGN) RCT filter. The search strategies for all databases can be found in Appendix 1.

### Data collection and analysis

#### Selection of studies

Records retrieved by the initial search were scanned by review authors (HV and JW) to exclude obviously irrelevant studies and to identify trials that met the inclusion criteria. Full-text articles were retrieved and reviewed independently for the purpose of applying the inclusion criteria. In all instances, differences of opinion were resolved by discussion.

#### Data extraction and management

We extracted data from the studies independently using standardised forms. All differences of opinion between the authors were resolved by discussion.

#### Assessment of risk of bias in included studies

We assessed the risk of bias for each study according to the recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2006).

The risk of bias tool incorporates assessment of randomisation (sequence generation and allocation concealment), blinding


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(of participants, treatment providers and outcome assessors), completeness of outcome data, selection of outcomes reported and other sources of bias. We considered assessors of clinical outcomes and assessors of histological findings after the biopsy separately in our assessment of blinding and completeness of outcome data. Discrepancies in ratings were resolved by discussion.

### Measures of treatment effect

We expressed dichotomous data as risk ratios (RR) and 95% confidence intervals (CIs). We expressed continuous data as mean differences (MD) and 95% CIs.

### Assessment of heterogeneity

We tested statistical heterogeneity using the $Chi^2$ test with significance at $P < 0.10$, and a quantification of the degree of heterogeneity using the $I^2$ statistic and further exploration using sensitivity analyses.

### Data synthesis

We planned all analyses to be made on data reported for intention-to-treat results. However, none of the studies used such analyses. We used the fixed-effect model to pool data where there was no evidence of significant heterogeneity between studies, and the random-effects model when such heterogeneity was present (DerSimonian 1986).

### Subgroup analysis and investigation of heterogeneity

No specific subgroup analyses were prespecified.

## RESULTS

## Description of studies

For further details of the included, excluded and ongoing trials, please see the Characteristics of included studies, the Characteristics of excluded studies and the Characteristics of ongoing studies.

### Results of the search

In our first update in 2006, four trials comparing ACI with any other type of cartilage repair surgery were included in the systematic review (Basad 2004; Bentley 2003; Horas 2003; Knutsen 2004). In the second update in 2010, we also included two new trials (Dozin 2005; Saris 2008), and one (Knutsen 2007) which was a longer-term follow-up of an already included trial (Knutsen 2004). We found another study previously categorised as excluded (Horas 2000) to be another publication of an already included trial (Horas 2003). In the current third update in 2011, searches were performed in January 2011. One trial report, previously in studies awaiting assessment, Basad 2010 was a full report of an already included trial (Basad 2004). Given that Basad 2010 reported a greater number of participants, with a more complete follow-up, we considered that this should be considered the definitive publication of this trial. A longer term follow-up of Saris 2008 was also included (Saris 2009). We also found two reports (Van Assche 2009; Van Assche 2010) that reported findings from a subgroup of trial participants of Saris 2008. Both Saris 2009 and Van Assche 2009 were in 'Studies awaiting assessment' in the previous version of the review.

In this update, seven other newly identified publications were excluded; two were abstract reports of the same trial (Park 2008) and one was a long term follow-up of an already excluded trial (Gudas 2005). Additionally, two more report of ongoing studies were identified (Fickert; SUMMIT extension study), the second being an extension study of SUMMIT.

### Included studies

#### *Design*

Of the six included trials, five were randomised trials and one (Horas 2003) was quasi-randomised.

Horas 2003 is the same study as Horas 2000 (formerly excluded as a non-randomised study in our review). Horas 2000 was not cited in the 2003 report, but the response of the trial authors to a letter (Smith 2003) commenting on Horas 2003 confirmed that "the same patient population formed the basis for both the German publication (Horas 2000) and the present article. However, different individual aspects of the treatment's results were highlighted, especially in the Discussion sections of the two articles". Both these articles report follow-up at 24 months. However, because of differences in the presentation of outcomes between the two main reports of Horas 2003 and the availability of raw data for Horas 2003, we chose only to review the 2003 report.

Knutsen 2007 is a five-year follow-up evaluation of Knutsen 2004, which reported on two-year follow-up after surgery in the 2004 article. As the information on the study design was better described in Knutsen 2004, we based the risk of bias assessment on this report.

Saris 2009 presented the 36 month follow-up of Saris 2008. Data from different follow-up times were extracted from both publications. Van Assche 2009 and Van Assche 2010 studied a subgroup of Saris 2008 from two centres (one Belgium and one Dutch).

Basad 2010 was a full report of Basad 2004. Basad 2010 was conducted in the same centre during the same time, and using the same follow-up time of two years. The authors included more participants and presented the outcomes in a more complete and relevant way. Therefore, we considered that Basad 2010 was the definitive report of this trial.

#### *Sample sizes*

The six included studies recruited a total of 442 participants. Based on reported allocation, 237 had one of the autologous chondrocyte implantation (ACI) techniques and 205 had either microfractures or mosaicplasty. In the former, 94 trial participants had ACI with the use of periosteum, 46 had ACI with the use of collagen membrane, 57 had characterised chondrocyte implantation (CCI) and 40 had matrix-guided ACI (MACI). Bentley 2003 assessed 58 ACI-treated participants, 12 of which had the technique with periosteum and 46 with collagen membrane as a coverage of the lesion area. In the control groups, 121 participants had microfractures and 84 had mosaicplasty.

#### *Setting*

Three trials were single-centre trials, two of which were based in Germany (Basad 2010;Horas 2003) and one in the UK (Bentley 2003). Dozin 2005 was a multi-centre study with three surgeons and involvement from five orthopaedic centres in Italy. Knutsen 2004 was a multi-centre study involving four centres in Norway and


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one in the UK. Saris 2008 was a multi-centre study undertaken in 13 centres in four countries (Belgium, Croatia, Germany and the Netherlands).

Saris 2008 was sponsored by TiGenix n.x. Eight authors of this study declared a conflict of interest. One or more of the authors in Bentley 2003 also declared a conflict of interest (details not provided).

### *Participants*

The participants of all the studies had isolated cartilage lesions of the femur or the patella. The average size of the lesions was homogenous, ranging between 3.8 $cm^2$ and 5.1 $cm^2$ for three trials (Bentley 2003; Horas 2003; Knutsen 2004). In Basad 2010, the acceptable size of the lesion for trial inclusion was between 4 $cm^2$ and 10 $cm^2$; however, Basad 2004 reported a lower limit of 2 $cm^2$. In Dozin 2005 and Saris 2008 , the size of treated lesions was much smaller: Dozin 2005 had an average size of 2.0 $cm^2$ and 1.9 $cm^2$ for ACI and mosaicplasty respectively, while the mean size of cartilage lesions in Saris 2008 was 2.5 $cm^2$.

There were important differences in the inclusion criteria of the included studies (*see* Characteristics of included studies). For example, Knutsen 2004 and Saris 2008 included only participants with femoral condyle lesions, while the other trials included lesions at other sites (mainly patella lesions). Cases with osteochondritis dissecans were excluded by Horas 2003 and Saris 2008 but were included in remaining trials. Osteochondral lesions were also withdrawn from Basad 2010. Concomitant lesions (anterior cruciate ligament ruptures or meniscal tears) were not excluded in Saris 2008. Acording to the protocol, Basad 2010 excluded patients with prior or planned meniscectomies (>30% of the meniscus) or knee instability. However, one microfracture patient had an ACL reconstruction. Five patients (two in the MACI and three in the microfracture group) had smaller meniscal lesions treated.

Other sources of between-trial variation included differences in the history of previous surgery and baseline clinical scores: for instance, the ACI group had a Lysholm score of 24.9 in Horas 2003 and 57.4 in Knutsen 2004.

The average ages of trial participants in the individual trials ranged between 29 years (Dozin 2005) and 34 years (Basad 2010; Saris 2008). All six trials (Basad 2010; Bentley 2003; Dozin 2005; Horas 2003; Knutsen 2004; Saris 2008) included more male than female participants (60% or more of all participants were males).

### *Interventions*

Four different comparisons were tested by the six included trials. Three trials compared ACI with mosaicplasty (Bentley 2003; Dozin 2005; Horas 2003). Dozin 2005 and Horas 2003 clarified that they used autologous periosteum for the coverage of the cartilage lesion and the implanted cells. In the ACI group, Bentley 2003 used either periosteum or collagen membrane. Knutsen 2004 compared ACI (using periosteum) versus microfractures. Basad 2010 compared MACI with microfractures and Saris 2008 compared characterised chondrocyte implantation (CCI) with microfractures.

Where described, the rehabilitation programmes differed between the studies (*see* the Characteristics of included studies). For example, Bentley 2003 used a cast to keep the knee in extension for the first 10 days, and encouraged full-weight bearing at 24 hours postoperatively. In contrast, Horas 2003 allowed flexion up to 90 degrees for the first 10 days with partial weight-bearing at two weeks and full weight-bearing at 12 weeks. Basad 2010 used a different rehabilitation program for each of the treatment groups.

### *Outcomes*

Several different outcomes were presented by the trials (Lysholm score, Tegner, modified Cincinnati, visual analogue scale (VAS) for pain, Mayes, KOOS: Knee Injury Osteoarthritis Outcome Score, patient rated ICRS and SF-36). Only Horas 2003 provided raw data of all the outcomes measured (Lysholm, Tegner, Meyers, complications). Knutsen 2004, and the longer term follow-up report (Knutsen 2007), presented histograms or box plots but not numerical data for functional and pain outcomes (Lysholm, VAS, SF-36). Although specified in the methods section, the Tegner score is not presented in Knutsen 2004 and only the mean baseline and final scores are presented in Knutsen 2007.

Four trials reported the Lysholm score. However, only Horas 2003 provided exact scores through raw data. Basad 2010 gave the mean values and standard deviations. Knutsen 2004 presented the results in a histogram, Dozin 2005 presented them in groups with cut points at 60 and 90.The Tegner score is presented by Basad 2010, Horas 2003 and in Knutsen 2007. VAS for pain and the SF-36 results are presented in Knutsen 2004 only. The Meyers score is presented by Horas 2003. KOOS is given only by Saris 2008.

Four trials also reported on a limited number of second-look arthroscopies, also providing results from biopsy of the repair tissue. Bentley 2003 and Knutsen 2004 provided the ICRS score based on the morphology of the repair tissue and also the quality of the repair tissue after a biopsy retrieval (categorised into hyaline-like, mixed, fibrocartilage or fibrous tissue). Horas 2003 gave a more case-based narrative description of some biopsies and Saris 2008 provided a mean histology score based on different features of the histological components of structural repair.

## Excluded studies

We excluded 21 studies. Detailed information is given in the Characteristics of excluded studies.

Ten of the excluded studies were RCTs. Six of these compared two different ACI techniques. Gooding 2006 and Zeifang 2010 compared ACI-P (use of periosteum) with ACI-C (use of collagen membrane instead of periosteum). Park 2008 compared ACI-P with MACI (matrix-guided ACI). Bartlett 2005 and Bickerstaff compared ACI-C with MACI. (The full manuscript of Bickerstaff could not be traced.) Schneider 2003 compared conventional ACI with another ACI technique (CaReS). Visna 2004 addressed a valid comparison for our review; they compared an ACI-based treatment (cultivated autologous chondrocytes in a three-dimensional carrier of fibrin glue) with abrasive techniques. However, 20% of the participants had double lesions and 10% had tibia plateau lesions, which was not consistent with our inclusion criteria. Gudas 2005 did not compare any ACI technique. Two RCTs (Ebert 2008; Wondrasch 2009) compared different rehabilitation approaches for patients treated with MACI.

Anderson 2003, Behrens 2006 and Kon 2009 were not RCTs, but prospective cohort studies.

Nine of the excluded studies could not be traced (Bickerstaff; Brittberg; Jacobsen; Joergensen; Keating; Trial 1; Trial 2; Trial 3;


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Trial 4). Seven of these were identified in a Health Technology Assessment systematic review (Jobanputra 2001) but remain untraceable (Brittberg; Jacobsen; Joergensen; Trial 1; Trial 2; Trial 3; Trial 4). At least two of the nine studies were industrially sponsored and at least three more studies were evaluating a product of interest to industry.

#### *Ongoing studies*

Detailed information for the ongoing studies is given in the Characteristics of ongoing studies.

We found eight ongoing studies evaluating ACI or other ACI-based techniques. Two evaluate conventional ACI (ACTIVE; Richardson), two evaluate CARTIPATCH (Barnouin; Dubrana), one evaluates NeoCart (Crawford), one evaluates MACI (SUMMIT), one evaluates the BioCart$^{TM}$II (Roth-Ben Arie), and one the co.Don Chondrosphere (Fickert). There are eight different comparisons: ACI versus any conventional technique (ACTIVE), ACI (NeoCart) versus microfracture (Crawford), ACI (MACI) versus microfracture (SUMMIT), ACI (BioCart TM II) versus microfracture (Roth-Ben Arie), ACI (CARTIPATCH®) versus microfracture (Barnouin), ACI (CARTIPATCH®) versus mosaicplasty (Dubrana), co.Don Chondrosphere versus microfracture (Fickert) and ACI and osteotomy versus osteotomy alone (Richardson). Five of these are multi-centre trials (ACTIVE; Dubrana; SUMMIT; Roth-Ben Arie; Fickert). Five studies are industrially sponsored (Barnouin; Crawford; SUMMIT; Roth-Ben Arie; Fickert).

According to the trial registration details, 1459 participants will be included, 660 of whom are in the ACTIVE study. One of the studies (Richardson) should have been finished in December 2007, but no publication of the results has been traced so far. For the rest, one trial is planned to finish in 2011, two in 2012, three (including the five-year follow-up of SUMMIT) in 2015 and two in 2016.

#### *New studies found for this update*

This update included one updated trial (Basad 2010), previously Basad 2004. Basad 2010 described a larger population with a fuller account of outcome at two years compared with Basad 2004. We considered that Basad 2010 is the definitive trial report of this trial. A longer term follow-up of Saris 2008 was also included (Saris 2009). We also found two more reports of RCTs ((Van Assche 2009; Van Assche 2010) that reported on the outcomes of a subgroup of trial participants of Saris 2008.

We also found two new reports of ongoing studies. One was new (Fickert) and the other (SUMMIT extension study) was a five-year follow-up study for patients who have completed the SUMMIT trial.

Five trials are newly excluded (Ebert 2008; Kon 2009; Park 2008; Wondrasch 2009; Zeifang 2010).

### Risk of bias in included studies

The results of the quality assessment are given in the Characteristics of included studies and summarised in Figure 1 and Figure 2. Additionally, a brief descriptive account of the studies is provided below.


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**Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.**

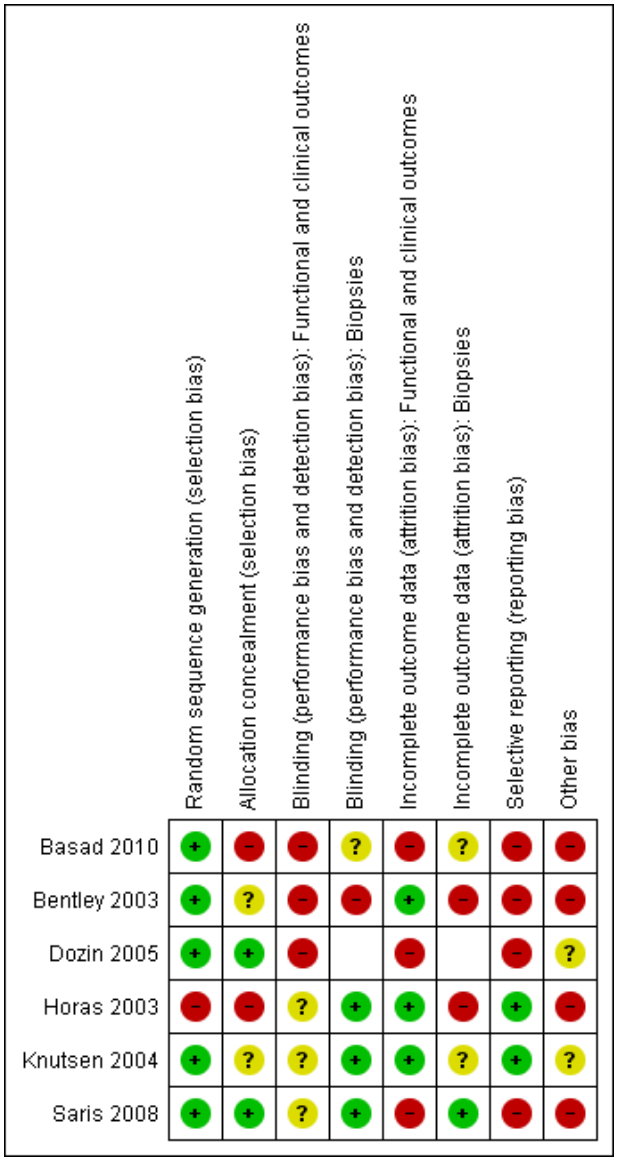



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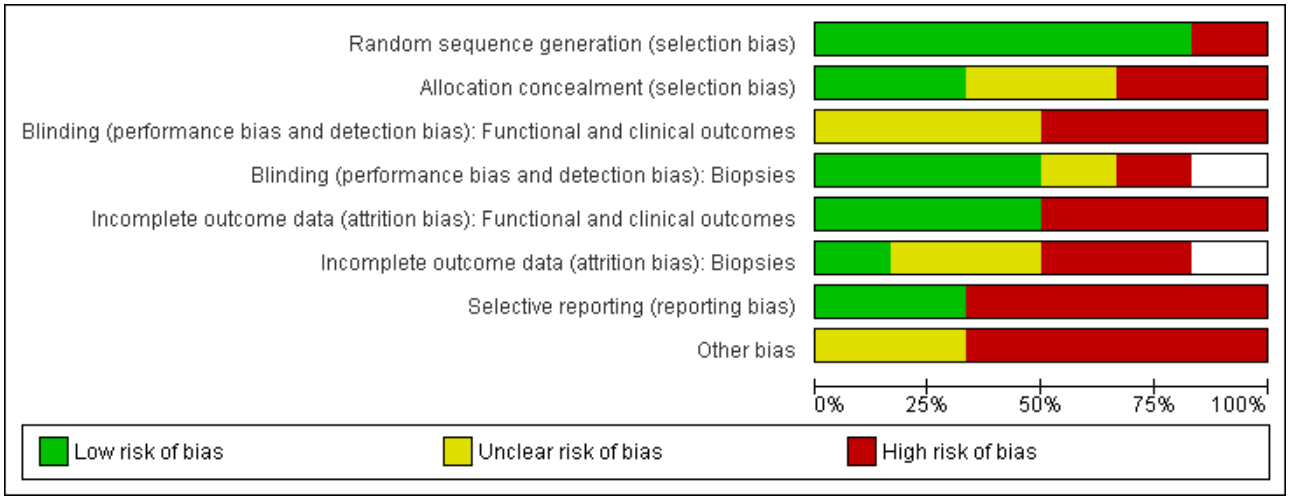
**Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.**




Whenever it was necessary, we contacted the contributing authors of the included trials by email in order to obtain further clarifications regarding the methodology followed in their trial. Where the authors' answers changed our judgement in the 'Risk of bias' table, we detail this in the Characteristics of included studies.

Note that risk of bias assessment for Knutsen 2004 and Saris 2008 is based on the detailed methodology provided in the 2004 and 2008 papers respectively. The methods given in the follow-up reports (Knutsen 2007; Saris 2009) are comparable. Basad 2010 has been primarily used for the risk of bias assessment of this trial but the methods reported in Basad 2004 were also referred to in our assessment.

### Allocation

Appropriate sequence generation to ensure randomisation seemed likely in all trials except Horas 2003, which was quasi-randomised. The methods of sequence generation were adequately described in the reports of three trials (Basad 2010; Dozin 2005; Saris 2008), but additional clarification provided by the corresponding authors of Bentley 2003 and Knutsen 2004 demonstrated the use of an adequate sequence generation method. Allocation concealment was adequate in two trials (Dozin 2005; Saris 2008), and unclear in another two (Bentley 2003; Knutsen 2004). Although sealed envelopes were used in Knutsen 2004, no additional information was given to specify if the envelopes were opaque. In the earlier report of Basad 2010, Basad 2004 reported that participants who did not agree with their allocated therapy were dropped out; thus the randomisation process was compromised and the trial was judged at a high risk of selection bias. Basad 2010 did not refer to this in their later report nor give any information regarding the allocation concealment. Horas 2003 used alternation, and thus allocation concealment was not possible in this trial.

### Blinding

Two of the studies did not provide enough information to determine the strategies used to blind participants or assessors of clinical outcomes (Horas 2003; Saris 2008). Knutsen 2004 stated that an independent observer performed the follow-up clinical examination. Outcome assessors were not blinded in the studies of Basad 2004, Bentley 2003 and Dozin 2005. Knutsen 2004 stated that an independent observer performed the follow-up clinical examinations, but did not describe blinded assessment. In the five years follow-up, the evaluation was carried out by the first author, cancelling the claim for assessor's independency. Hence, the judgement is 'unclear' regarding risk of bias for this trial. Basad 2010 did not give additional information regarding blinding of the assessors.

We should probably acknowledge here the difficulty of blinding of the clinical outcomes assessors, that reflects the nature of the surgical interventions. Furthermore, it should be acknowledged that the only clinical outcomes assessed in the trials were patient-derived scores, thus no clinical assessors were needed.

Three trials (Horas 2003; Knutsen 2004; Saris 2008) reported blinded assessment of overall histological assessment scores.

### Incomplete outcome data

In most studies, the number of participants who deviated from the study protocol was not reported. None of the patients were lost to the clinical follow-up in Bentley 2003 and Horas 2003. Dozin 2005 provides details on participants lost to follow-up, however the number is high. The authors reported that 22.7% (5.22) of the ACI and 31% (7/22) of the mosaicplasty allocated patients did not proceed to the operation due to spontaneous improvement after the first surgery and debridement of the defect area. Six of the patients allocated to the CCI arm of Saris 2008 did not have the intervention because of a negative ChondroCelect score that meant that the implant was not viable. Saris 2008 included these patients when presenting data on complications, but they did not include them in the results for treatment failure or for assessment of functional outcome using the KOOS score. Regarding histological assessment carried out in for trial, only Saris 2008 gave adequate information. Bentley 2003 and Horas 2003 only assessed a subgroup of participants; while 16% (13/80) of patients did not have biopsies in Knutsen 2004.

Confirmation that no trial participants were lost from follow-up was received for Knutsen 2004. In the five-year follow-up analyses of this trial (Knutsen 2007), the patients with failure remained in the trial,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"with their last recorded clinical follow-up scores before the failure considered to be their final clinical score."

Bias resulting from incomplete data seemed high in Basad 2010, when based on an assessment of Basad 2004, where firstly an unknown number of participants who did not agree with their allocation were excluded, and secondly a large number of patients were lost to follow-up. In Basad 2010, there was fewer patients lost to follow-up compared with Basad 2004. There was, however, no intention-to-treat analysis and we considered that the risk of attrition bias remained high.

#### Selective reporting

Only two of the studies were judged free of selective reporting (Horas 2003; Knutsen 2004). The outcomes were presented in an insufficient way by Bentley 2003 did not present the Stanmore scores. Although the Meyers score was included in the protocol of Basad 2004, it was not presented in either Basad 2004 or Basad 2010. Lysholm scores were modified and provided at 12 months only in Dozin 2005, while no International Knee Documentation Committee data were provided. Saris 2008 presented KOOS score modified by removing the "sport" domain.

#### Other potential sources of bias

Horas 2003 gave a graph of the outcomes (figure 1 in the study report). However, although this study and Horas 2000 are duplicates, the same graph presented in Horas 2000 is slightly different (crossing of lines of Lysholm and Tegner in Horas 2000 but not in Horas 2003).The authors failed to explain this difference in their reply to the letter of Smith 2003. Although there are no significant differences in the outcomes, this is considered a questionable issue that potentially suggests bias. Basad 2010 was the full report of Basad 2004, reporting on the same follow-up time (two years). Although Basad 2004 had a large number of participants lost to follow-up (only 19 (41%) were available at one year follow-up and only five (11%) at two years), this is not the case in the later publication.

Rehabilitation differed considerably between trials. However, where described in the trial reports, the same programme was provided to both intervention groups of individual trials with the exception of Basad 2010.

#### *Sponsorship - conflict of interest*

The trial of Saris 2008 was sponsored by TiGenix n.x. TiGenix is the company that produces the ChondroCelect, the cell therapy product which is necessary for the CCI technique. Moreover, eight authors including the two lead authors of this study declared a conflict of interest. One or more of the authors in Bentley 2003 also declared a conflict of interest (no details provided).

#### *Patient baseline characteristics*

Treatment groups were similar at baseline with respect to defect size and level of function in four studies (Dozin 2005; Horas 2003; Knutsen 2004; Saris 2008).

The defect lesion size was reported in all studies. The interim report of Basad 2010 (Basad 2004) reported differences in the size of defect at baseline with no further details. However, in Basad 2010 the only difference was the prolonged symptom duration of MF treated patients, which was 0.3 years longer than in the MACI group.

All trials had clear inclusion and exclusion criteria and there was some consistency between studies. Within the studies, participants were generally well matched for location and size of defect lesion, although Saris 2008 reports that proportionally more participants in the comparator group had undergone previous knee surgery.

### Effects of interventions

The four comparisons tested by one or more of the six included trials are presented separately below. The three studies testing the same comparison (ACI versus mosaicplasty) were sufficiently dissimilar to merit separate descriptions. Only one, primarily exploratory, meta-analysis was performed.

#### ACI versus mosaicplasty

Bentley 2003 found no statistically significant differences in functional assessment at one year using either the modified Cincinnati or Stanmore scores (Cincinnati score ("excellent" or "good" results): ACI 51/58 (88%) versus mosaicplasty 29/42 (69%), (reported P = 0.277)). However, our analysis found a statistically significant result for excellent and good results that favours ACI over mosaicplasty (risk ratio (RR) 1.27, 95% confidence interval (CI) 1.02 to 1.59; *see* Analysis 1.1). A post-hoc subgroup analysis by defect site was reported by Bentley 2003 to show a statistically significant difference in function in the ACI group at one year only for participants with lesions of the medial femoral condyle (Cincinnati score "excellent" or "good": ACI 21/24 (88%) versus mosaicplasty 21/29 (74%), reported P = 0.032). Cincinnati scores were not statistically significantly different in people with either lateral femoral condyle or patellar defects.

After one year follow-up, International Cartilage Repair Society (ICRS) grades of 1 (excellent) or 2 (good) assessed using arthroscopy were given to 30/37 (82%) after ACI and 8/23 (34%) after mosaicplasty; RR 2.33, 95% CI 1.30 to 4.17 (*see* Analysis 1.2). In "50%" of participants of the ACI group, tissues were relatively soft on probing compared with the surrounding cartilage. Seven out of 19 participants who had biopsies after ACI at one year were found to have hyaline cartilage of normal appearance. The number of participants having biopsy after mosaicplasty was not stated and results were only reported for seven participants with a Cincinnati scale rating of "poor". In four of these participants, the plugs were *in situ* but the tissue between them had not become covered with continuous fibrous tissue; in three, the plugs had disintegrated; and in one participant, the area of the mosaicplasty had remained reasonably intact but the articular cartilage at the margins of the defect had broken down to expose subchondral bone. Bentley 2003 shown an improvement of the quality of the repair tissue of an ACI patient between a biopsy taken at one and another at two years. This interesting finding suggests an ongoing maturation of the repair tissue over time.

Bentley 2003 reported complications but did not mention whether any further surgery was required. Moreover, the authors did not split the complications by treatment group. In total, one participant developed calf-vein thrombosis and required anticoagulants and one developed a superficial infection. Three of the participants were slow to mobilise and required manipulation under anaesthesia; one of these required arthroscopy and arthrolysis to mobilise the knee.

Horas 2003 found statistically significant differences in Lysholm scores at six, 12 and 24 months favouring the mosaicplasty group


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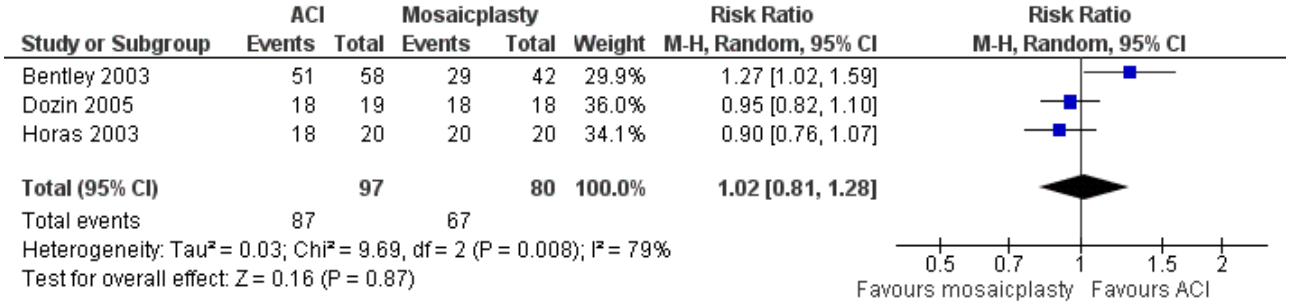
(45.75 versus 53.45 at six months; 57.50 versus 68.25 at 12 months and 66.75 versus 72.70 at 24 months; see Analysis 1.3, results derived from the published raw data for this trial). It is notable that at 24 months postoperatively, 18 of the 20 ACI group participants and all of the 20 mosaicplasty group participants had a Lysholm score of 60 or more, which is considered the threshold for a 'good' result. The investigators found no significant difference between ACI and mosaicplasty for any time period when participants were assessed using the Tegner or the Meyers scores. The Tegner scores for ACI versus mosaicplasty were 1.55 versus 1.55 at three months, 2.95 versus 3.55 at six months, 4.25 versus 5.00 at 12 months and 5.10 versus 5.20 at 24 months (*see* Analysis 1.4). The Meyers scores for ACI versus mosaicplasty were 8.50 versus 7.85 at three months, 12.05 versus 13.75 at six months, 14.15 versus 15.90 at 12 months and 15.90 versus 16.75 at 24 months (*see* Analysis 1.5).

The proportions of participants with complications reported in Horas 2003 were the same in both groups at 24 months (ACI 12/20 (60%) versus mosaicplasty 12/20 (60%)). In both groups, complications were either surgical (i.e. locking of the joint and adhesions) or non-surgical (i.e. passing irritation of the infrapatellar branch of the saphenous nerve) and variable in nature. Similar numbers of participants (8 versus 9) in the two groups had a subsequent surgical procedure, predominantly involving arthroscopy. However, most operations in the ACI group were to rectify longer term complications (range of timing of operations 2 to 24 months) whereas those in the mosaicplasty group generally occurred sooner after the operation (range 4 days to 22 months) and included treatment for haemarthrosis in two participants.

Dozin 2005 found no significant differences in overall functional assessment and clinical evaluation using the Lysholm Knee Scoring Scale (LKSS) and the Standard International Knee Documentation Committee Evaluation Form. The LKSS ratings were categorised as complete success (> 90), partial success (60 to 90) or failure (< 60). Fifteen of the 22 ACI-treated patients (68.2%) and 17 of the 22 mosaicplasty-treated patients (77.3%) had a Lysholm score of 60 or more. When combined with symptom disappearance to allow for a clearer comparison of the outcome in the two treatment arms, the percentage of complete success was 68.4% (13/19) for ACI versus 88.9% (16/18) for mosaicplasty (RR 0.77, 95% CI 0.54 to 1.09; *see* Analysis 1.6). No adverse events were reported.

Although outcome measurement differed in the three trials, and the categorisation of continuous scales into crude categories is generally unsatisfactory; two analyses featuring all three trials are presented on an exploratory basis. Analysis 1.6 presenting results for an 'excellent' outcome shows the disparity between the results of the three trials. Analysis 1.7 shows the pooled results for "satisfactory outcome of success". This is based on the "excellent and good results" retrieved from the Cincinnati score as presented by Bentley 2003 and also by the "partial and complete success" as presented by Dozin 2005 (patients with final Lysholm score of 60 or more with consecutive report of clinical improvement). Partial and complete success was derived from the raw data provided by Horas 2003 and was defined as a Lysholm score of 60 or more. The analysis revealed a non-significant result, with no preference to one treatment over the other (Figure 3), but also considerable heterogeneity ($I^2$ = 79%).

**Figure 3. Forest plot of comparison: 1 ACI versus mosaicplasty, outcome: 1.7 Satisfactory outcome (various criteria) - exploratory analysis.**




**ACI versus microfracture**

Knutsen 2004 found an improvement after both interventions (ACI and microfracture) at one, two and five years postoperatively. In both trial reports, the authors presented the majority of the results graphically, without giving the exact numbers. In Knutsen 2004, the mean values could be extracted from the plots; these are given below. This was not possible for the five-year follow-up report (Knutsen 2007).

The authors found that the two intervention groups did not differ significantly with regards to the Lysholm score and pain score, assessed using the visual analogue scale (VAS), at all follow-ups. Mean baseline Lysholm scores were similar in the two groups (ACI: 57.4 versus microfracture: 55.4), and improved in both groups at one year (ACI: 69.2 versus microfracture: 78) but not at two years (ACI: 70.8 versus microfracture: 75.4).

The Tegner score also showed no statistically significant difference between the groups in all time points. Based on the physical component of the Short Form-36 in the first two years, the microfracture group improved significantly more than the ACI group (reported P = 0.004). No such difference was found at five years follow-up (reported P = 0.054). The authors reported a significant improvement of SF-36 from baseline to five years for the microfracture group but not for the ACI group. However, the baseline scores were different (reported P = 0.05), which was not addressed in the analysis of the results. SF-36 physical scores changed from 41.1 (baseline) to 42.6 at one year and 42 at two years for the ACI group, and from 37.4 (baseline) to 42.9 and 46 at one and two years respectively in microfracture group (Analysis 5.10). No difference was detected two years postoperatively in the SF-36 mental health domain. In the microfracture group, patients who had lesions smaller that 4 $cm^2$ were reported to have had significantly better clinical results (according to the Lysholm score,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VAS and SF-36) than those with a bigger defect (P < 0.003). Such an association was not apparent in the ACI group.

Arthroscopy conducted two years after surgery did not show any difference between the ACI and microfracture groups using the ICRS grading system; the findings were graded as "nearly normal" in both groups. Of the 67 biopsies obtained, the difference in presence of some hyaline cartilage between the two groups was not statistically significant (16/32 versus 10/35; RR 1.75, 95% CI 0.93 to 3.28; *see* Analysis 2.1).

Two years postoperatively, there were two "failures" (5%) in the ACI group and one (3%) in the microfracture group (*see* Analysis 2.2). Knutsen 2004 defined a failure as requiring "a re-operation because of symptoms due to a lack of healing of the primary treated defect. The need for shaving or trimming a lesion was not defined as a failure." These participants received another cartilage treatment and were excluded from further follow-up. Further arthroscopic surgery for trimming and shaving was needed in 10 cases in the ACI group (25%) and four (10%) in the microfracture group. In ACI participants, shaving was usually required for symptomatic tissue hypertrophy. Among microfracture participants, one participant had adhesions needing manipulation and operative release, and three had minor debridement. No serious complications, such as deep infections or thromboembolic events, were reported. Five years after the surgery, the authors report nine failures, including one total knee replacement, in each treatment group (Knutsen 2007) (*see* Analysis 2.2).

**MACI (matrix-guided ACI) versus microfracture**

Basad 2010 found that while participants in both groups had better Lysholm, Tegner and patient ICRS scores than at baseline, the improvements were greater for the MACI group and had persisted at 24 months follow-up. Differences between the two groups in the mean Lysholm scores were not statistically significant at six (87 versus 82) or 12 months (92 versus 82) but were significant at 24 months, reflecting a decline in the scores of the microfracture group (92 versus 69; MD 23.00, 95% CI 9.49 to 36.51; see Analysis 3.1). Participants in the microfracture group also showed a much broader scattering of results.

A similar pattern was apparent for level of activities as measured by Tegner score. The MACI group had statistically significantly better Tegner score results at 24 months (MD 0.65, 95% CI 0.12 to 1.18; *see* Analysis 3.2). Although more participants of the MACI group achieved an ICRS subjective score group of either 1 or 2 compared with those in the microfracture group at 24 months (28/30 versus 6/10, RR 1.56, 95% CI 0.93 to 2.60; *see* Analysis 3.3), the reduction in the study population available for this outcome measure was not explained.

No data were available for complications; however, the authors stated that there were no treatment-related safety issues during the study. One participant of the MACI group had persistent pain and persistent subchondral oedema; the pain was resolved by retrograde bone grafting.

**Characterised chondrocyte implantation *(CCI)* versus microfracture (MF)**

Saris 2008 did not show a significant difference (either statistical or clinical) between the two treatments in the "overall" KOOS (Knee Injury Osteoarthritis Outcome Score) scores at six, 12 or 18 months (*see* Analysis 4.1). Some caution should be exercised in interpreting these results as the authors elected to exclude one of the five components of the KOOS score (the 'sports' domain) due to inadequate data. Additionally, the data for six participants of the CCI group who (due to low score of chondrogenic potential) did not receive allocated treatment and those for two protocol violations in the microfracture group were not included. In the 36 months follow-up the authors presented the mean improvement from baseline. Sports domain data of KOOS were also reported at 36 months but still not included in the overall KOOS scores. The mean improvement from baseline in overall KOOS at 36 months was greater with CCI compared with microfracture but did not reach statistical significance (MD 5.42, 95% CI -4.39 to 15.23, see Analysis 4.2. Note that there are discrepancies in the numbers available at follow-up for this outcome. Based on a 'mixed linear model approach', with time as a categorical variable, the mean improvement from baseline results become statistically significant (MD 7.66, 95% CI 0.16 to 15.15; see Analysis 4.3). The better KOOS results for MACI were reflected in improvements over all five KOOS domains (*see* Analysis 4.2). In their 2009 publication, Saris 2008 found that, based on six monthly assessment intervals, the KOOS scores from baseline in the MACI group continued to improve over time, whereas those in the microfracture group did not, appearing to plateau or decline after 18 months.

Saris 2008 conducted post-hoc subgroup analyses of the overall KOOS scores at 36 months follow-up based on time since onset of symptoms, with results presented for two subgroups of participants with symptoms onset before two years and before three years respectively. However, these results were incompletely reported with no indication of the numbers of participants in each group.

Saris 2008 reported fewer treatment failures, who had subsequently undergone re-intervention, at 36 months in the CCI group but the difference between the two groups was not statistically significant (2/51 versus 7/61, RR 0.34, 95% CI 0.07 to 1.57; see Analysis 4.4). Moreover, this does not include the six CCI participants who did not receive treatment and who thus can be considered treatment failures also for this group.

At 18 months, the numbers of participants reporting adverse events, both overall (CCI: 50/57 (88%) versus MF: 50/61 (82%)) and those considered related to the study procedures (CCI: 38/57 (67%) versus MF: 36/61 (61%)) were similar in the two groups. Seven of the CCI participants (12%) and eight of the microfracture participants (13%) reported serious adverse events, while five (9%) and eight (13%), respectively, were considered related to the allocated surgery. However, no criteria were given for the determination of serious adverse events. Two adverse events considered related to the study procedure that required hospitalisation occurred in the CCI group. These were one case of deep vein thrombosis occurring 19 days after surgery and one case of severe tendinitis of the fascia lata occurring approximately 18 months after surgery. The data for overall and some individual treatment-related adverse events at 18 months are presented in Analysis 4.5; and at 36 months in Analysis 4.6. In both treatment groups, arthralgia (joint pain) was the most commonly reported adverse event, with no statistically significant difference between the two groups (RR 1.07, 95% CI 0.79 to 1.44 at 18 months and RR 0.99, 95% CI 0.65 to 1.51 at 36 months). More participants in the CCI group experienced joint swelling occurring within 14 days postoperatively (RR 3.92, 95%


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CI 1.15 to 13.35: *see* Analysis 4.5), but difference between the two groups in joint swelling was not statistically significant at 36 months. Joint crepitations were more common in the CCI group than the microfracture group; this reached statistical significance at 36 months (RR 4.82, 95% CI 1.09 to 21.35; *see* Analysis 4.6).

Van Assche 2009 and Van Assche 2010 assessed the recovery of physical activity levels after surgery in a subgroup of 67 of the 118 participants of Saris 2008 who were based in Belgium and Dutch centres. The authors reported a decrease in functional performance at six months following CCI which resulted in slower recovery at 9 and 12 months compared with microfracture. However, by two years follow-up, CCI patients had similar overall functional outcome compared with microfracture patients. These studies reported no significant difference between the treatment groups in ‘‘overall’’ sports participation at two years, as assessed by the Modified Baecke Sport Index scores. However, MF-treated patients showed a significant decrease in Activity Rating Scale (ARS) scores at one year and two years after surgery. The CCI-treated patients did not show a significant change in ARS scores.

# DISCUSSION

## Summary of main results

This review included data from six trials, involving a total of 442 participants, comparing ACI with a number of different procedures such as mosaicplasty and microfracture. The heterogeneity of the trials, especially in the interventions compared and outcomes, precluded pooling, except on an exploratory basis. Hence, there is very limited evidence available on which to judge the effectiveness of ACI for treating full thickness articular cartilage defects of the knee.

### ACI versus mosaicplasty

The three trials for this comparison reported contradictory findings for functional outcome. While Bentley 2003 found the statistically significant results in favour of ACI for people with 'excellent' or 'good' modified Cincinnati scores, the analysis of Lysholm score data provided for Horas 2003 found in favour of the mosaicplasty group. However, there was no significant difference between groups in the numbers of participants with a good outcome nor was there in functional outcome measured using the Meyers or Tegner scores. Dozin 2005 found no statistically significant differences between the two groups for functional outcomes. Pooled data from measures of "satisfactory outcome" demonstrate this variation in the results of the three trials (Analysis 1.7).

Only Bentley 2003 reported statistically significant results in favour of ACI based on ICRS grades of "good" or "excellent" following arthroscopy at one year. However, only 30% of the total number of randomised participants received arthroscopy and the lack of blinding also increases the risk of bias in these findings.

Bentley 2003 failed to indicate the treatment group of the five participants with complications, one of which required arthroscopy. Sixty per cent of participants in both groups had a variety of complications in Horas 2003, whereas no adverse events were reported in Dozin 2005.

### ACI versus microfracture

Knutsen 2004 reported no significant differences between the two groups in function measured via the Lysholm and Tegner scores or in pain at follow-up. The difference in favour of the microfracture group in SF-36 physical domain results at two-year follow-up was reported as not statistically significant at five years. Similar numbers in both groups were deemed 'failures' at two and five years. Arthroscopic examination at two years yielded "nearly normal" findings for both groups. Although more ACI group participants had presence of hyaline cartilage at biopsy, the difference between the two groups was not statistically significant.

### MACI (matrix-guided ACI) versus microfracture

One trial (Basad 2010) compared MACI versus microfracture. At 24 months, the Lysholm and Tegner scores were significantly better in the MACI group compared with the microfracture group. Notably, the results for the MACI improved over time whereas those from the microfracture group had deteriorated between 12 and 24 months. There was no detailed reporting of adverse effects for this trial. It is important to mention that Basad 2010 used a different rehabilitation program appropriate for each of the treatment groups.

### Characterised chondrocyte implantation (CCI) versus microfracture

The one trial making this comparison (Saris 2008) found no significant differences between the two treatments in the knee function at 6, 12 or 24 months follow-up; however, there was a greater improvement in clinical outcomes at 36 months. The authors also found that improvement continued for the CCI group from 24 to 36 months; while the MF group reached a plateau after 18 months postoperatively.

Similar numbers of participants of the two groups had treatment-related adverse events at 18 and 38 months. While the number of participants with joint pain were similar in the two groups at both follow-up times, significantly more in the CCI group reported postoperative swelling, and there was greater incidence of joint crepitation after CCI.

## Overall completeness and applicability of evidence

The heterogeneity of the available evidence has been referred to above. In addition, there was a reduction in the available evidence resulting from loss to follow-up, non-participation in subsequent invasive procedures, such as biopsies, and post-randomisation exclusions. There is also potential loss of evidence from unreported trials. As we mentioned in the Excluded studies, nine trials could not be traced so far. Seven of these were identified in a Health Technology Assessment systematic review in 2001 (Jobanputra 2001) but still could not be traced. According to their protocols, most of these studies would be included in this review and thus provide important evidence to judge the effectiveness of ACI over other treatments. However, it seems that these trials were either abandoned due to organising or participating issues or the results were never published, suggesting a publication bias.

The favourable findings of small, single-centre trials should be considered provisional and requiring confirmation from other larger, and preferably multi-centre trials. However, some noteworthy points arise still from the individual trials in terms of applicability. For instance, it should be noted that Horas 2003


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did not use fibrin glue for the watertight seal of the periosteal patch, which was against the recommendations of the inventors of the technique (Brittberg 1994). However, there is no evidence to attribute the slightly inferior results of the ACI group to cell leakage; and studies would be needed to evaluate the need, if any, of the extra procedure.

Based on post-hoc subgroup analysis, the trials provided some preliminary evidence that the location and size of the defect may be important. Bentley 2003 found more favourable results for ACI in participants with medial condylar defects. Knutsen 2004 found that the microfracture technique had poorer results in lesions over 4 $cm^2$. This finding was consistent with the results of Gudas 2005 who reduced this size limit to 2 $cm^2$. It seems that there is evidence to support the suggestion that small lesions may heal spontaneously or after bone marrow-stimulating procedures (Steadman 2003). The small size of cartilage lesions in Dozin 2005 may explain the high rate of spontaneous improvement and high rate of symptom relief (and withdrawal from the study) after the first surgery and debridement of the chondral lesion. There is evidence to support that a more clear distribution of indications of each of the cartilage lesion treatments should be performed. The results given above should be further investigated and confirmed with additional studies so to potentially conclude in defining specific indications. However, it is important to note the tentative nature of these findings so far, which should also be set in the context of the basic question examined in this review.

Saris 2008 showed a continuous improvement after 18 months, up to at least 36 months, although the microfracture group reached a plateau in terms of clinical function after 18 months. In Basad 2010, the Lysholm score similarly declined for the microfracture group between 12 and 24 months; the MACI group shown a stable score after 12 months. Those two studies may provide evidence for a more stable and long standing outcome after ACI compared with microfracture; the latter may not provide sufficiently high quality repair tissue that can resists wear and tear over time. The finding is also compatible with the suggestion of that hyaline cartilage may mature even 1.5 or 2 years after the surgery (Bentley 2003; Brun 2008; Peterson 2000).

Based on post-hoc and inadequately reported subgroup analyses involving an unspecified number of participants, Saris 2008 reported significantly better improvement in overall KOOS results at 36 months follow-up for CCI patients whose onset of symptoms was less than three years before treatment. Notably, similar findings for the subgroup of patients whose onset of symptoms was less than two years did not reach statistical significance. The dangers of subgroup analyses are rife (Sun 2010) and it is essential that the claims in Saris 2009 of a time to treatment effect are not taken as proven. Another issue that is still questioned and needs to be clarified is the potential effect of previously performed subchondral bone surgeries on the outcome after an ACI treatment. Although the outcomes were not systematically reported, MRI evaluation in Saris 2008 revealed a "subchondral bone reaction" in both CCI and microfracture groups. However the microfracture treated patients developed more subchondral bone reaction with more extended elevation of the subchondral bone, 36 months postoperatively. No clinical association was searched by the authors. This finding is compatible with others showing that ACI treated patients that had a previous history of microfracture of the lesion, had a higher incidence of intralesional osteophytes in the long term (Vasiliadis 2010a). Cohort studies have also suggested that there was a negative clinical effect on patients treated with ACI, when they had previously treated with microfracture (Bartlett 2005; Minas 2009). Thus along with the time of surgery, history of previous surgery may also play an additional role for the success of the ACI treatment. More studies are needed to confirm or reject those suggestions.

Most of the included trials failed to present the adverse effects or failures of the interventions. Where evidence is available, ACI seems to result in a similar incidence of adverse events and failures to other methods but the information given is too limited to confirm this.

Bentley 2003 provided some evidence showing that there is an ongoing maturation of the repair tissue even two years postoperatively after ACI; and Knutsen 2004 found a greater tendency for hyaline cartilage after ACI at two years. There are studies to show that the potential of the repair tissue after any cartilage treatment may change over time due to subsequent maturation (Roberts 2003). Studies have also shown that after microfracture, patients' knees may deteriorate over time due to failure of the repair tissue (Kreuz 2006). Thus, there are questions regarding the adequate timing for biopsies, if strictly necessary, for the evaluation of the treatment outcome and for the longest follow-up time which is appropriate for assessing the final outcome of the treatment. The findings of similar numbers of people in the two treatment groups with 'treatment failure', including one in each group having undergone total knee replacement at five years follow-up of Knutsen 2004, show the importance of longer-term follow-up.

Notably, there are limitations of the biopsy as an evaluation tool for the assessment of the effectiveness of a cartilage treatment therapy. There is no evidence that a biopsy cylinder that is histologically proved to consist of hyaline tissue mechanically behaves as normal cartilage. Another issue is whether a small cylinder taken from the repair tissue can predict the consistency, integration and mechanical behaviour of the entire lesion (Vasiliadis 2010a). It is also questionable whether it is ethically correct to sacrifice a part of the repair tissue in order to assess its quality. Even if the retrieved tissue is relatively small, it may affect the patient's clinical status in the future. This concern, and the reluctance of asymptomatic participants to provide consent for biopsy at one year, formed the basis for a change in protocol in Basad 2010 to the non-collection of these samples.

There is a notable heterogeneity among the studies comparing an ACI technique with other treatments. Among the six studies, there were four different ACI techniques evaluated (ACI-P, ACI-C, MACI, CCI) which were compared with two different interventions (mosaicplasty and microfracture). Besides that, there were several outcomes assessed and questionnaires were often presented in different ways (values or groups of values). Therefore there was a limited opportunity for pooling and to present a meta-analysis of the outcomes. As a result, the amount of information is not adequate to draw a safe conclusion regarding the effectiveness of the ACI over other treatments.

This is a request then for more homogenous studies in the future. However, it seems that the launching of new materials in the market makes the interventions even more heterogeneous. In the seven ongoing studies, there are seven different comparisons (*see* the


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Characteristics of ongoing studies). There are also three products to be compared for the first time in a RCT, and all of them will be compared with microfracture. The only way to produce a valuable conclusion regarding the superiority or not of ACI, would be the pooling of all ACI techniques or at least of the third generation ACI techniques. Another interesting finding is that four of the ongoing studies are industrially sponsored (Barnouin; Crawford; Roth-Ben Arie; SUMMIT); all four studies compare a specific product of the sponsoring company with microfracture.

### Quality of the evidence

The quality of the individual studies is detailed in the 'Risk of bias' tables in the Characteristics of included studies and presented visually in Figure 1 and Figure 2. Only one trial (Knutsen 2004) was judged as being at low or unclear risk of bias for the items assessed. A high risk of selection bias resulting from compromised randomisation methods was evident in the earlier reports for Basad 2010 due to post-randomisation exclusions; although these were not mentioned in full report of this trial (Basad 2010), we consider this is still of concern. Horas 2003, which was quasi-randomised, was also judged at high risk of selection bias. While assessor blinding, where done, was limited to the examination of biopsy findings, it should be noted that outcome was mainly assessed using patient-derived scores. Patients could not be blinded due to different incisions of ACI treatment and microfractures (only scars from arthroscopy apparent) or mosaicplasty (lack of scar for periosteal retrieval).

An important flaw of the studies is the large proportion of missing data and also the failure to address incomplete outcome data. In all but one of the studies (Dozin 2005), details on the outcomes from patients who deviated from the study protocol or were lost to clinical follow-up were not reported. That was even more obvious for the arthroscopic evaluation and biopsies as an outcome (in four studies). Except in one study (Saris 2008) there was not an organised recruitment of the participants. Only a limited number of the patients were biopsied and there was no reference to any criteria for this. Therefore, the validity of finding for this outcome should be considered doubtful. There was evidence of selective reporting in most of the studies and also some potential for other bias. At least in two of the trials, industrial sponsorship was involved (Bentley 2003; Saris 2008); both favoured the ACI intervention.

Given the above, we can conclude that the evidence provided is of relatively limited validity.

### Potential biases in the review process

The comprehensive search undertaken, including for ongoing trials, and the return to trial authors for further details of their studies should have helped reduce publication and reporting biases. One of the authors (HV) is undertaking clinical and basic research in ACI. However, as the review process was carried out independently by two investigators, it is unlikely that this would introduce bias in the review.

### Agreements and disagreements with other studies or reviews

There are three recently published systematic reviews addressing RCTs examining the use of autologous chondrocyte implantation for treating articular cartilage knee defects (Bekkers 2009; Vasiliadis 2010b; Vavken 2010). Bekkers 2009 includes four RCTs that compared ACI versus microfracture or mosaicplasty. Bekkers 2009 is partly focused on possible selection criteria for the treatment selection of full thickness cartilage lesions of the knee. However, the limited number of published high quality, level one, relevant studies does not allow for safe conclusions. Vasiliadis 2010b is a systematic review based on this one, thus following the Cochrane methodology; it also includes three studies that compared different ACI techniques. Vavken 2010 included also studies comparing ACI versus any other treatment and also comparisons between different ACI techniques. In Vavken 2010, Horas 2000 and Horas 2003 were assessed as individual studies, thus overestimating the outcomes of this study (Vasiliadis 2010d). This systematic review also concluded that there is much inconsistency in methodological quality and findings among the included studies which precludes drawing. All the above mentioned systematic reviews agree with our main findings.

Harris 2010 included 13 studies of Level I or II evidence (i.e. additionally included prospective cohort studies ), comparing ACI with microfracture or mosaicplasty with other ACI techniques (2nd or 3rd generation ACI). The authors also concluded that additional high quality studies are needed to draw safe conclusions regarding any superiority of ACI.

Another older systematic review (Ruano-Ravina 2006) included three RCTs and nine case series comparing ACI to other treatment. The authors concluded that available data afforded no evidence that ACI is more effective than other conventional techniques in treating chondral lesions of the knee. Another systematic review (Clar 2005), which included four RCTs as well as observational studies, also suggested that "there is insufficient evidence at present to say that ACI is cost-effective compared with microfracture or mosaicplasty. Longer term outcomes are required". The authors suggested that "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)". Currently there is no evidence to confirm this hypothesis.

## AUTHORS' CONCLUSIONS

### Implications for practice

There is insufficient evidence from the six trials included in this review to conclude whether autologous cartilage implantation is superior to other treatment strategies for treating full thickness articular cartilage defects in the knee.

### Implications for research

Given the use of ACI and other chondral resurfacing techniques is becoming increasingly widespread, there is a strong case for further randomised trials of high methodological rigour and long-term follow-up of functional outcomes in order to determine the effectiveness of ACI for participants with knee defects. Specifically, more information and research is needed to compare chondrocyte techniques with conservative treatment such as intensive physiotherapy. Further information is needed on the relationship between clinical, histological and radiological outcomes, and the most appropriate measure of functional outcomes that relate to a generic measure of health-related quality


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of life. The regular updating of this review is also required as new evidence becomes available.

## ACKNOWLEDGEMENTS

The authors would like to thank Joanne Elliott for her guidance and contribution to the development of the search strategies, and feedback on referencing.

The authors would also like to acknowledge the contributing authors of Basad 2010, Bentley 2003, Knutsen 2004 and Saris 2008 for providing additional information, upon our request, on their trials.

2010 update: We would like to pay tribute to the contributions of Christine Clar and Elmer Villanueva, authors of the original review. They were unable to participate in this update. The authors would also like to thank Peter Herbison, Janet Wale and Paresh Jobanputra for valuable comments about this version of the review. In particular, we thank Helen Handoll for very useful comments that greatly improved earlier versions of this update. We also acknowledge Lesley Gillespie for her guidance and contribution to the development of the search strategies, and feedback on referencing.


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* Indicates the major publication for the study


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## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

#### Basad 2010

| | |
|---|---|
| Methods | Randomised controlled trial. Patients were allocated with consecutive numbers in the order of their study entry and then randomised via computer generated randomisation list. There was no blinding of participants or outcome assessors. Single centre study conducted in Germany. |
| Participants | 60 participants (40 MACI, 20 microfractures) (mean age 34.2 years; range of defect size from 4 to 10 $cm^2$) with a post-traumatic, single, symptomatic lesion of the articular cartilage in the knee.<br><br>In Basad 2004; 46 participants (mean age 33 years; range of defect size from 2 to 10 $cm^2$) with a post-traumatic, single, symptomatic lesion of the articular cartilage in the knee suitable for cartilage repair. Nineteen patients participated in 12-month follow-up (10 MACI, 9 microfracture), whilst only 5 participated at 24 months. |
| Interventions | Matrix-guided ACI (MACI) versus microfracture<br><br>A different rehabilitation programme was used for each of the treatment groups. |
| Outcomes | Follow-up: at 3, 6, 12, 18 and 24 months<br>1. Lysholm-Gillquist score<br>2. Tegner-Lysholm score<br>3. ICRS (International Cartilage Repair Society) score (patient and surgeon scores) |
| Notes | Two different MACI™ membranes, from two different manufacturing sites were used for the MACI group. Half of the patients received each of the different membranes.<br><br>Biopsies were not taken although intended in the protocol. The authors explain that it was due to biopsy site morbidity in the first two cases, as shown on the MRI, and reluctance to give consent from participants with asymptomatic knees. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | A computer generated randomisation list was used. |
| Allocation concealment (selection bias) | High risk | Patients were allocated with consecutive numbers in the order of the study entry. The authors do not clarify the method of allocation concealment.<br><br>In Basad 2004, the authors stated that "after the participants signed the written informed consent an envelope with the randomisation number was opened. Patients who didn't agree with their therapy dropped out" |
| Blinding (performance bias and detection bias) Functional and clinical outcomes | High risk | No description provided in the Basad 2004 or Basad 2010 papers. However after personal communication the authors stated that "the outcome assessors were not blinded" |
| Blinding (performance bias and detection bias) Biopsies | Unclear risk | No description provided in the Basad 2004 or Basad 2010 papers. However after personal communication the authors stated that "the outcome assessors were not blinded" |
| Incomplete outcome data (attrition bias) Functional and clinical outcomes | High risk | In Basad 2004, it was reported that participants who did not agree with their allocated therapy were excluded. 19 participated in 12-month follow-up, whilst only 5 participated at 24 months |


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**Basad 2010** *(Continued)*

| | | |
|---|---|---|
| | | Although the authors state in Basad 2010 that they had several missing values, they do not perform an intention-to-treat analysis. |
| Incomplete outcome data (attrition bias) Biopsies | Unclear risk | Not performed |
| Selective reporting (reporting bias) | High risk | Biopsies not taken, although included in the protocol.<br><br>Meyers score was referred to Basad 2004, although it was not evident in the methods of Basad 2010. |
| Other bias | High risk | The study seems to be an extended version of Basad 2004 with the same follow up time (2 years). Although Basad 2004 had a large number of participants lost to follow-up (only 19 (41%) were available at one year follow-up and only five (11%) at two years), this is not the case in the full report of the trial in 2010.<br><br>Additionally, the lower limit of the range of defect size was 2 $cm^2$ in Basad 2004 and 4 $cm^2$ in Basad 2010. |

**Bentley 2003**

| | |
|---|---|
| Methods | Randomised controlled trial. Allocation concealment not clear (sealed envelopes were prepared), randomisation was computer-generated (personal communication). There was no blinding of participants or outcome assessors (personal communication). Single centre study conducted in the UK. |
| Participants | 100 participants aged between 16 to 49 years (mean age 31.3 years; 57% male; range of defect size from 1.22 to 12.2 $cm^2$, mean 4.66 $cm^2$) with symptomatic lesion of the articular cartilage in the knee suitable for cartilage repair (osteochondral or chondral defect of more that one centimetre in diameter in a joint that was otherwise biomechanically normal and free from inflammatory disease). Participants had cartilage defects of varying aetiologies: trauma 46%, osteochondritis dissecans 19%, chondromalacia patellae 14%, and other, probably post-traumatic, 21%. Cartilage defects were at various sites (median femoral condyle 53%, patella 25%, lateral femoral condyle 18%, trochlea 3% and lateral tibial condyle 1%). Surgery was considered appropriate for participants with persistent pain and reduction in activities. All but 6 participants had undergone previous surgical interventions, although all had undergone arthroscopy with the mean number of further operations at 1.5. No details were given on the types of previous operations. |
| Interventions | ACI (with use of periosteum or collagen membrane) versus mosaicplasty<br><br>After surgery, a cast was used to keep the knee in extension for the first 10 days, and full-weight bearing was encouraged at 24 hours postoperatively. Light jogging could commence at 6 months but no sports activities were allowed during the first year |
| Outcomes | Follow-up: at 12 months<br>1. Clinical improvement rated by the modified Cincinnati rating system and the Stanmore functional rating system: excellent (at least 80), good (55 to 79), fair (30 to 45) or poor (< 30) based on the Cincinnati Rating System. Improvement defined as excellent or good results.<br>2. Arthroscopy used to assess repair according to the International Cartilage Research Society (ICRS) grading system |
| Notes | ACI was performed with 2 different methods. Some of the patients were treated with the use of periosteum for the coverage of the cartilage lesion and the injected suspension of cells (ACI-P). For the rest of the patients a collagen membrane was used instead of the autologous periosteal patch (ACI-C). All those patients were summarised into the ACI arm which was compared with mosaicplasty. |
| ***Risk of bias*** | |


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**Bentley 2003** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | According to the paper, it is unclear due to lack of description. However, after personal communication the authors replied that "the randomisation was done by a computer". |
| Allocation concealment (selection bias) | Unclear risk | Sealed envelopes were prepared, but no further information given as whether opaque or not. (Although the imbalance in numbers between the 2 groups (58 versus 42) is striking, this may have occurred randomly.) |
| Blinding (performance bias and detection bias) Functional and clinical outcomes | High risk | No information given on patient and outcome assessor blinding from the paper. However the authors clarified that "the assessors were not blinded to the operation performed" |
| Blinding (performance bias and detection bias) Biopsies | High risk | No report on blinding in the paper. However the authors clarified that "the assessors were not blinded to the operation performed". |
| Incomplete outcome data (attrition bias) Functional and clinical outcomes | Low risk | The authors did not report any lost to follow-up patients for the clinical assessment |
| Incomplete outcome data (attrition bias) Biopsies | High risk | Only 19 biopsies were taken from the ACI group. The number of participants having biopsy after mosaicplasty was not stated, results being reported only for 7 participants with a poor Cincinnati scale rating. |
| Selective reporting (reporting bias) | High risk | Stanmore scores data not provided. Authors report that scores were similar to the modified Cincinnati Knee Scale score. |
| Other bias | High risk | Study reports the use of ACI-P and ACI-C as one procedure. No information is given for how it was decided if the first or the latter technique was to be used.<br><br>One or more of the authors declared a conflict of interest |

**Dozin 2005**

| | |
|---|---|
| Methods | Randomised controlled trial. Method of randomisation: random permuted blocks. Allocation concealment stated (use of central telephone facility). Blinding of participants investigators and outcome assessors not reported. No intention-to-treat analysis. Multi-centre study with 3 surgeons and contribution of 5 orthopaedic centres in Italy. |
| Participants | 47 participants (16 to 40 years of age) with a cartilaginous lesion presenting a focal symptomatic chondral injury of III or IV Outerbridge grade without subchondral bone injury or loss; traumatic or micro-traumatic injury as diagnosed by arthroscopy and/or nuclear magnetic resonance; symptoms characterised by episodes of pain and/or swelling and no previous surgical treatment (debridement, abrasion, arthroplasty, drilling and/or microfracture). Overweight participants with associated injury to or loss of subchondral bone, knee joint instability, associated meniscus damage, injured anterior cruciate ligament etc. were excluded.<br><br>Of 44 participants, mean age 29 years; males: 61%. Seventy per cent of the lesions were localised on the femoral condyle (84% medial condyle and 16% lateral condyle) and 30% on the patella. The severity of the lesions was of III grade in 23% of the cases and of IV grade in the remaining 77%, as evaluated at the arthroscopic examination.<br><br>Twenty-three participants received allocated surgery |


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**Dozin 2005** *(Continued)*

| | |
|---|---|
| Interventions | ACI with use of periosteum versus mosaicplasty |
| Outcomes | Follow-up: at 1, 2, 3, 6, 12, 24 and 36 months (scheduled)<br>1. Lysholm Knee Scoring Scale<br>2. Standard International Knee Documentation Committee Evaluation Form |
| Notes | 47 were initially registered (ACI 22, MP 25). Two of the mosaicplasty group were excluded due to malfunction in randomisation and 1 refused mosaicplasty. Twenty-one more were lost (14 were improved after the debridement, 2 refused due to personal reasons (pregnancy, change of surgeon), 5 did not show up in the pre-surgery examination and could not be traced). So finally there were 12 participants allocated ACI and 11 allocated MP who received these interventions.<br><br>There was poor compliance with follow-up and the reported results were nominally for 12 months (primary endpoint) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random lists stratified by orthopaedic surgeon and balanced in permuted blocks of varying block size in random sequence |
| Allocation concealment (selection bias) | Low risk | Central telephone randomisation procedure |
| Blinding (performance bias and detection bias) Functional and clinical outcomes | High risk | Participants and outcome assessors not blind to treatment. The clinical evaluations were performed by their own surgeons. |
| Incomplete outcome data (attrition bias) Functional and clinical outcomes | High risk | Considerable missing data. Intention-to-treat analysis not performed. Missing values at 12 months replaced by last observation. |
| Selective reporting (reporting bias) | High risk | Lysholm scores modified and provided at 12 months only. Data for Standard International Knee Documentation Committee evaluation not provided. |
| Other bias | Unclear risk | Insufficient information to assess whether another important risk of bias exists |

**Horas 2003**

| | |
|---|---|
| Methods | Quasi-randomised controlled trial. Allocation concealment unlikely, treatment allocated using alternative consecutive selection, blinding of participants or outcome assessors not reported. |
| Participants | 40 participants were included in the study. Twenty patients (12 women and 8 men) with a mean age of 31.4 years (range: 18 to 42 years) were treated with ACI. Twenty patients (5 women and 15 men) with a mean age of 35.4 years (range: 21 to 44 years) were treated with transplantation of an OCT. The sizes of the cartilage lesions ranged from 3.2 to 5.6 $cm^2$ (mean, 3.75 $cm^2$) in the series as a whole, 3.86 $cm^2$ in the group treated with ACI and 3.63 $cm^2$ in the group treated with OCT. Cartilage defects existed at various sites for those randomly assigned to ACI (median femoral condyle 85%, lateral femoral condyle 15%) and OCT (median femoral condyle 80%, trochlea 3% and lateral tibial condyle 1%). Forty per cent of the participants had previous surgery that included arthroscopy alone (5% of all participants), abrasion (20%), drilling (2.5%), extraction of osteochondral bodies (5%) and incomplete resection of the medial meniscus (7.5%). Some participants had more than one type of surgery. |


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**Horas 2003** *(Continued)*

| | |
|---|---|
| Interventions | ACI with use of periosteum versus osteochondral cylinder transplantation (OCT)<br><br>After surgery, flexion up to 90 degrees was allowed for the first 10 days with partial weight-bearing at 2 weeks and full weight-bearing at 12 weeks |
| Outcomes | Follow-up: at 6, 12 and 24 months<br>1. Lysholm score<br>2. Meyers score<br>3. Tegner score<br><br>Histomorphological evaluations of biopsy specimens within 2 years of ACI |
| Notes | No bio-glue was used for the ACI (water sealing was achieved only with sutures) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Quasi-randomised study. Group assignment using alternating consecutive selection |
| Allocation concealment (selection bias) | High risk | The allocation was based on alternation of consecutively admitted patients |
| Blinding (performance bias and detection bias) Functional and clinical outcomes | Unclear risk | Information regarding patient and outcome assessor blinding was not reported |
| Blinding (performance bias and detection bias) Biopsies | Low risk | The authors mention that the histologist was blinded with regard to patient allocation |
| Incomplete outcome data (attrition bias) Functional and clinical outcomes | Low risk | None of the trial participants was lost to the follow-up |
| Incomplete outcome data (attrition bias) Biopsies | High risk | Only a few participants who had had an arthroscopy also had a biopsy. No rating scheme was given and no statistical analysis performed on the biopsy results (descriptive presentation). |
| Selective reporting (reporting bias) | Low risk | All the outcomes mentioned in the methods were finally addressed in the results |
| Other bias | High risk | There is a difference in the outcomes' graphs in this study and Horas 2000, although those 2 studies are supposed to be the same. The authors failed to explain this difference in their reply to the letter of Smith 2003. |

**Knutsen 2004**

| | |
|---|---|
| Methods | Randomised controlled trial. Allocation concealment stated (use of sealed envelopes), block randomisation was used (personal communication). Clinical outcome assessors were blinded to treatment group. Histological assessment was blinded too. No blinding of clinical assessors in 5-year follow-up (Knutsen 2007). A multi-centre study performed in 4 centres in Norway and 1 in the UK. |


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**Knutsen 2004** *(Continued)*

| | |
|---|---|
| Participants | 80 participants (mean age 32.3 years; 60% males) with a history of a single symptomatic cartilage defect on the femoral condyle in a stable knee. 40 allocated to ACI and 40 to microfracture (mean, 33.3 and 31.1 years respectively, defect size mean, 5.1 $cm^2$ and 4.5 $cm^2$, respectively). Each had cartilage defects of varying aetiologies: trauma 65% or osteochondritis dissecans 28%. Defects were located predominately on the median femoral condyle (89%) with 11% located on the lateral femoral condyle. Nearly all participants (94%) had previous surgery including: arthroscopic lavage and debridement (36%), anterior cruciate ligament reconstruction (19%); meniscal surgery (18%), Pridie drilling (4%) and operations for osteochondritis dissecans such as drilling or fixation of a fragment (16%). The patients treated with ACI had undergone an average of 1.6 previous surgical procedures to treat the cartilage defect, and those in the MF group had undergone an average of 1.4. |
| Interventions | ACI with use of periosteum (ACI-P) versus microfracture<br><br>After surgery: continuous passive motion and partial weight-bearing with crutches were started on the first postoperative day. The patients then remained partially weight-bearing for 8 weeks. Full weight-bearing was introduced between 8 and 12 weeks postoperatively. |
| Outcomes | Follow-up at 1, 2 and 5 years:<br>1. Lysholm score<br>2. Tegner score<br>3. Visual analogue scale (VAS) pain score<br>4. Short Form-36 (SF-36)<br>5. 'Failure' and additional procedures<br><br>Arthroscopic evaluation and histomorphological evaluations of biopsy specimens within 2 years of surgery. |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | According to the paper, it is unclear due to lack of description. However, after personal communication the authors replied that "block randomisation" was used. |
| Allocation concealment (selection bias) | Unclear risk | Reported use of sealed envelopes, but no other description provided regarding if they were opaque or not |
| Blinding (performance bias and detection bias) Functional and clinical outcomes | Unclear risk | Independent outcome assessor performed follow-up at clinical examination<br><br>However, the 5-year follow-up evaluation (Knutsen 2007) was carried out from the first author, cancelling the claim for assessor's independency |
| Blinding (performance bias and detection bias) Biopsies | Low risk | Histology assessment and evaluation undertaken by blind assessors |
| Incomplete outcome data (attrition bias) Functional and clinical outcomes | Low risk | No information given regarding any missing data for the clinical evaluation in the paper. However, after personal communication, the authors confirmed that "No patients were lost to follow-up".<br><br>While clinical data were not collected from the 9 failures in each group at 5 years, this loss to follow-up is balanced and may not have resulted in bias |
| Incomplete outcome data (attrition bias) Biopsies | Unclear risk | Thirteen patients did not have a biopsy at 2 years (8 with ACI, 5 with MF). Missing data from these may affect the results. |


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**Knutsen 2004** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | All the outcomes are presented in the results |
| Other bias | Unclear risk | Insufficient information to assess whether an important risk of bias exists |

**Saris 2008**

| | |
|---|---|
| Methods | Randomised controlled trial. Method of randomisation: minimisation method. Allocation concealment and blinding of participants and investigators not reported. Outcome assessors blinded. Intention-to-treat analysis not performed. A multi-centre study conducted in 13 centres in 4 countries (Belgium, Croatia, Germany and the Netherlands). |
| Participants | 118 participants (18 to 50 years of age) with symptomatic single femoral cartilage lesion between 1 $cm^2$ and 5 $cm^2$. Participants with recent osteochondritis dissecans (< 1 year), microfractures (< 1 year ago), instability, malalignment or extended meniscal resections (> 50%) were excluded. Mean age 34 years, 64% male. Seven of the patients had also an anterior cruciate ligament (ACL) lesion, 6 had a meniscal lesion and 2 had both ACL and meniscal lesion. In the CCI group, 5 patients had previous microfracture and 3 had previous subchondral drilling. In the microfracture group, 1 patient had previous microfracture and 2 had previous subchondral drilling. In addition, 1 patient in each group had previous abrasion arthroplasty. |
| Interventions | Characterised chondrocyte implantation (CCI) versus microfracture<br><br>After surgery: partial weight-bearing allowed after 2 weeks and full weight-bearing, as tolerated, at 6 weeks. Low impact training was initiated at 10 months and high-impact training after 16 months. |
| Outcomes | Follow-up: at 6, 12,18 and 36 months<br>1. Knee Injury and Osteoarthritis Outcome Scores (KOOS) (symptoms, stiffness, pain, activities of daily living, functions in sports, quality of life, overall scoring)<br>2. Adverse events<br><br>Biopsy and histology analysis at 12 months |
| Notes | The CCI technique is performed as the conventional ACI with periosteum (ACI-P), but with the use of selected-characterised chondrocytes. Characterised chondrocytes are an expanded population of chondrocytes that expresses a marker profile (a gene score) potentially predictive of the capacity to form hyaline-like cartilage in vivo.<br><br>Each biopsy is graded with a ChondroCelect score (CC score). CC score is based on the quantitative gene expression of a selection of positive and negative markers developed to predict the cells' ability to form stable hyaline cartilage in vivo.<br><br>Additional outcome data presented for 2 centres by Van Assche 2009 and Van Assche 2010. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Minimisation method was used to achieve treatment balance with respect to operation surgeon, location of lesion and presence or absence of associated lesions |
| Allocation concealment (selection bias) | Low risk | Randomisation was done at the time of surgery, just after the cartilage defect inspection |
| Blinding (performance bias and detection bias) | Unclear risk | No information given regarding the blinding of the assessors of clinical outcomes |


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| | | |
|---|---|---|
| **Saris 2008** *(Continued)*<br>Functional and clinical outcomes | | |
| Blinding (performance bias and detection bias)<br>Biopsies | Low risk | The overall histology assessment scores were determined by 2 blinded histopathologists |
| Incomplete outcome data (attrition bias)<br>Functional and clinical outcomes | High risk | Six participants of the CCI group did not receive allocated treatment because of negative ChondroCelect score and were not included in the outcomes. Two protocol violations in microfracture group. |
| Incomplete outcome data (attrition bias)<br>Biopsies | Low risk | Missing data balanced across groups |
| Selective reporting (reporting bias) | High risk | Primary outcome measure was modified by removing the 'sport' domain |
| Other bias | High risk | Possible reporting bias regarding the adverse events. Assessors were not blinded and they were required to assign a causal relationship to the procedure (CCI or microfracture).<br><br>The trial was sponsored by TiGenix n.x. Eight authors declared a conflict of interest. |

ACI: autologous cartilage implantation
ACL: anterior cruciate ligament
CCI: characterised chondrocyte implantation
ICRS: the International Cartilage Repair Society's cartilage injury evaluation package
MACI: matrix-guided autologous cartilage implantation
MF: microfracture
OCT: osteochondral cylinder transplantation

**Characteristics of excluded studies** *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Anderson 2003 | Not an RCT. |
| Bartlett 2005 | RCT comparing the use of porcine-derived type I/type III collagen as a cover (ACI-C) with MACI using a collagen bilayer seeded with chondrocytes. Does not meet the inclusion criteria of ACI versus no treatment, placebo or a form of standard treatment. |
| Behrens 2006 | Not an RCT. It is a prospective clinical study of MACI treated patients. |
| Bickerstaff | No full manuscript could be traced. The trial should have finished by 1 December 2006. RCT comparing the use of MACI with collagen-covered autologous chondrocyte implantation. Does not meet the inclusion criteria of ACI versus no treatment, placebo or a form of standard treatment. |
| Brittberg | Unable to trace this trial<br><br>Trial (located in Göteborg, Sweden) of unknown name. Identified in 2001 in a Health Technology Assessment systematic review. Sixty participants in total: 30 to undergo subchondral drilling with periosteal flap and 30 to receive ACI. No further details available. |


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| Study | Reason for exclusion |
|---|---|
| Ebert 2008 | RCT comparing traditional versus accelerated approaches to post-operative rehabilitation following MACI. Does not meet the inclusion criteria of ACI versus any other treatment. |
| Gooding 2006 | RCT comparing the use of periosteal covered ACI versus type I/type III collagen covered ACI (ACI-C). Does not meet the inclusion criteria of ACI versus no treatment, placebo or a form of standard treatment. |
| Gudas 2005 | RCT that compares mosaicplasty versus microfracture. Does not compare ACI. |
| Jacobsen | Unable to trace this trial.<br><br>Trial (located in Siegsle, Denmark) of unknown name or number identified in 2001 in a Health Technology Assessment systematic review. Forty participants in total: MACI versus microfracture. No further details available. |
| Joergensen | Unable to trace this trial.<br><br>Multi-centre trial (located in Denmark) of unknown name or number identified in 2001 in a Health Technology Assessment systematic review. Comparison of ACI, surgical debridement and mosaicplasty for lesions less than 2 $cm^2$. No further details available. |
| Keating | Unable to trace this trial. The trial should have finished by 30 June 2005. |
| Kon 2009 | Not an RCT. Cohort study comparing 2nd generation ACI with microfracture. Not randomised. |
| Park 2008 | RCT comparing ACI versus MACI. Does not meet the inclusion criteria of ACI versus no treatment, placebo or a form of standard treatment (abstract). |
| Schneider 2003 | RCT comparing ACI versus CaReS (cartilage regeneration system where chondrocytes are grown directly in a collagen gel). Does not meet the inclusion criteria of ACI versus no treatment, placebo or a form of standard treatment. |
| Trial 1 | Unable to trace this trial.<br><br>Multi-centre trial (located in USA) of unknown name or number identified in 2001 in a Health Technology Assessment systematic review. Eighty participants in total: 40 to receive ACI (Carticel) and 40 to receive periosteal graft without chondrocytes. No further details available. |
| Trial 2 | Unable to trace this trial.<br><br>Trial (located in Austria, Italy and Germany) of unknown name or number identified in 2001 in a Health Technology Assessment systematic review. Three hundred participants in total: MACI versus other treatments, including mosaicplasty and microfracture. No further details available. |
| Trial 3 | Unable to trace this trial<br><br>Trial (located in Malmoe University, Sweden) of unknown name or number identified in 2001 in a Health Technology Assessment systematic review. Eighty participants in total: 40 to receive ACI (in-house technique), 20 to undergo periosteal grafting without chondrocytes and 20 to receive surgical debridement. No further details available. |
| Trial 4 | Unable to trace this trial.<br><br>Multi-centre trial (located in USA) of unknown name or number identified in 2001 in a Health Technology Assessment systematic review. Three hundred participants in total: 150 to receive ACT (Carticel) and 150 to undergo subchondral drilling/microfracture. No further details available. |
| Visna 2004 | Patient characteristics do not meet the inclusion criteria. The study was a RCT comparing an ACI-based treatment (cultivated autologous chondrocytes in a 3-dimensional carrier–fibrin glue) with |


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| Study | Reason for exclusion |
|---|---|
| | abrasive techniques. However, this trial included a large variety of patients; 20% of the participants presented with double cartilage lesions, 10% with tibia plateau lesions, 20% requiring ACL reconstruction, 46% with partial meniscectomies and 12% meniscal suturing. No separation of the participants with femoral and patellar lesions was possible. |
| Wondrasch 2009 | RCT comparing the outcomes of MACI after accelerated weightbearing group (group A) vs delayed weightbearing (group B). Does not meet the inclusion criteria of ACI versus any other treatment. |
| Zeifang 2010 | RCT comparing the use of periosteal covered ACI versus type I/type III collagen covered ACI (ACI-C). Does not meet the inclusion criteria of ACI versus no treatment, placebo or a form of standard treatment. |

ACI: autologous cartilage implantation
ACT: autologous cartilage transplantation
MACI: matrix-associated autologous chondrocyte implantation
RCT: randomised controlled trial

**Characteristics of ongoing studies** *[ordered by study ID]*

**ACTIVE**

| | |
|---|---|
| Trial name or title | Autologous chondrocyte transplantation/implantation versus existing treatments (ACTIVE) |
| Methods | Multi-centre randomised controlled trial, with 24 centres in UK and 2 in Norway (as detailed in the trial website on 31 May 2010) |
| Participants | 330 ACI<br>330 "conventional" treatment |
| Interventions | ACI versus one of the following "conventional" treatments (debridement, abrasion, drilling, microfracture, or mosaicplasty) chosen by the surgeon/patient |
| Outcomes | Time to cessation of benefit: as defined when 2/3 assessment criteria show no improvement compared with preoperative assessment levels at least 12 months after surgery:<br>1. Independently assessed Lysholm Knee score<br>2. Patient self-assessed Lysholm Knee questionnaire<br>3. Independent assessor's judgement based on impact on quality of life, physical examination and functional observation<br>4. Cost-effectiveness |
| Starting date | February 2004 to March 2016 |
| Contact information | Prof James Richardson<br>Institute of Orthopaedics<br>The Robert Jones & Agnes Hunt Orthopaedic Hospital<br>Oswestry<br>SY10 7AG<br>UK<br>Phone: +44 (0)1691 404386 |
| Notes | Several UK centres registered the trial separately in the now archived National Research Register as participating centres of a multi-centre trial |


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**Barnouin**

| | |
|---|---|
| Trial name or title | Comparison of microfracture treatment and CARTIPATCH® chondrocyte graft treatment in femoral condyle lesions |
| Methods | Randomised controlled trial, probably single centre, Belgium |
| Participants | 64 (age 18 to 45 years) with isolated femoral osteochondral lesion (grade 3 or 4 lesion (ICRS) sized 2.5 to 7.5 $cm^2$; lesion depth under 10 mm), IKDC score below 55, no prior surgical treatment |
| Interventions | Autologous chondrocyte implantation (CARTIPATCH® procedure) versus microfracture |
| Outcomes | IKDC (18 months) |
| Starting date | October 2008 to December 2011 |
| Contact information | Contact: Laurence Barnouin +33 (0)4 72 68 69 01; laurence.barnouin@tbf-lab.com |
| Notes | Sponsored by TBF Genie Tissulaire |

**Crawford**

| | |
|---|---|
| Trial name or title | A randomised comparison of NeoCart to microfracture for the repair of articular cartilage injuries in the knee |
| Methods | Randomised controlled trial, 3 centres in USA |
| Participants | 245 participants, aged 18 years to 55 years, with symptomatic articular cartilage lesion of the femur. No prior surgical intervention other than debridement. |
| Interventions | NeoCart versus microfracture |
| Outcomes | Follow up: 1 year<br>KOOS, IKDC, MRI |
| Starting date | March 2010 to March 2015 |
| Contact information | Histogenics (Theresa G Wingrove, Ph.D. VP Clinical & Regulatory Affairs) |
| Notes | Sponsored by Histogenics Corporation |

**Dubrana**

| | |
|---|---|
| Trial name or title | Comparison of autologous chondrocyte implantation versus mosaicplasty: a randomized trial (Cartipatch) |
| Methods | Multi-centre RCT involving 12 centres in France |
| Participants | 76 (age 18 to 50 years) with isolated femoral osteochondral lesion (grade 3 or 4 lesion (ICRS) sized 2.5 to 7.5 $cm^2$), IKDC score below 55 |
| Interventions | ACI versus mosaicplasty |
| Outcomes | Follow-up: 2 years<br>IKDC |


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**Dubrana** *(Continued)*

| | |
|---|---|
| | MRI (2 years)<br>Arthroscopy and biopsy (2 years) |
| Starting date | April 2007 to July 2012 |
| Contact information | F Dubrana, MD, PhD, +33 298347566; frederic.dubrana@chu-brest.fr |
| Notes | University Hospital, Brest<br>Institut National de la Sante et de la Recherche Medicale, France |

**Fickert**

| | |
|---|---|
| Trial name or title | Efficacy and safety study of co.Don Chondrosphere to treat cartilage defects |
| Methods | Multicentre RCT involving 11 centres in Germany |
| Participants | 150 participants, aged 18 to 50 year, with isolated femoral osteochondral lesion (grade III or IV lesion (ICRS) sized 1 to < 4 $cm^2$ after debridement to healthy cartilage up to 6 mm in depth). |
| Interventions | Autologous Chondrocyte Transplantation product co.Don Chondrosphere (ACT3D-CS) versus microfracture |
| Outcomes | Follow-up: 12, 36, 48, 60 months<br>Change of overall KOOS<br>Change of the 5 subscores of the KOOS<br>MOCART<br>Bern Score and additional histological assessment scores<br>Change of ICRS/IKDC<br>Change of modified Lysholm Score<br>Days of absence from work (employment) and/or days of inability to follow usual activities<br>Frequence and type of adverse Events |
| Starting date | October 2010 to July 2016 |
| Contact information | Stefan Fickert, Ph.D., Universitatsmedizin Mannheim |
| Notes | Sponsored by co.don® AG |

**Richardson**

| | |
|---|---|
| Trial name or title | Autologous chondrocyte implantation in the treatment of early osteoarthritis |
| Methods | Randomised controlled trial, probably single centre, UK |
| Participants | 80 with symptomatic bone of bone cartilage defects |
| Interventions | ACI and osteotomy versus osteotomy alone |


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**Richardson** *(Continued)*

| | |
|---|---|
| Outcomes | Knee function and quality of life indicators |
| Starting date | September 2003 to December 2007 |
| Contact information | Prof James Richardson<br>Institute of Orthopaedics<br>The Robert Jones & Agnes Hunt Orthopaedic Hospital<br>Oswestry<br>SY10 7AG<br>UK<br>Phone: +44 (0)1691 404386 |
| Notes | Study completed but not published so far |

**Roth-Ben Arie**

| | |
|---|---|
| Trial name or title | Phase II study to investigate the efficacy and safety of BioCart$^{TM}$II in the treatment of symptomatic cartilage defects of the femoral condyle in comparison with microfracture |
| Methods | Multicentre randomised controlled trial with participating centres in USA and Israel |
| Participants | 40 participants, aged 16 to 60 years, with a single contained femoral condyle lesion (medial, lateral or trochlea) which is symptomatic (moderate to severe pain on VAS) and caused by trauma or osteochondritis dissecans. Depth of lesion up to 6 mm and size 1.5 to 7.5 $cm^2$ |
| Interventions | BioCart TM II versus microfracture |
| Outcomes | Follow-up: 12 months with optional follow-up to 5 years<br><br>Lysholm joint function score, IKDC, KOOS, ICRS functional status, VAS pain score |
| Starting date | May 2008 to May 2015 |
| Contact information | Zipi Roth-Ben Arie, PhD , + 972 8 9303021; zipi.benarie@prochon.co.il |
| Notes | Sponsored by ProChon Biotech Ltd |

**SUMMIT**

| | |
|---|---|
| Trial name or title | A prospective, randomised, open-label, parallel-group, multi-centre study to demonstrate the superiority of matrix-induced autologous chondrocyte implantation (MACI®) versus arthroscopic microfracture for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea |
| Methods | Multicentre, randomised controlled trial with centres in Czech Republic, France, Netherlands, Norway, Poland, Sweden, UK |
| Participants | 144 participants, age 18 to 55 years, with symptomatic articular cartilage defects in the knee |
| Interventions | Matrix-Induced Autologous Chondrocyte Implant (MACI® Implant) versus microfracture |
| Outcomes | Primary outcome measures (1 year): KOOS pain score and function score<br>Secondary outcome measures: histological score (1 year), MRI assessment (week 52 and 104) |


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**SUMMIT** *(Continued)*

| | |
|---|---|
| Starting date | July 2008 to March 2012 |
| Contact information | +1 617 252 7832; medinfo@genzyme.com |
| Notes | Sponsored by Genzyme<br><br>**Follow-on study**<br><br>An extension study for this trial is now registered: "An extension protocol for patients who completed Genzyme-sponsored prospective, randomized, open-label, parallel-group, multicenter study of matrix-induced autologous chondrocyte implantation (MACI® Implant) for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea"<br><br>**Outcomes**<br><br>Follow-up: 5 years<br><br>Change from baseline in overall KOOS and subscales<br><br>Treatment failures<br><br>Change from baseline in International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form<br><br>Change from baseline in the 12-Item Short-Form Health Survey (SF-12)<br><br>Change from baseline in the European Quality of Life (EuroQOL)<br><br>Number of participants reporting treatment-emergent adverse events<br><br>Number of participants reporting serious adverse events (SAEs)<br><br>Number of participants having subsequent surgical procedures (SSPs)<br><br>**Starting date**<br><br>November 2010 to February 2015<br><br>**Contact information**<br><br>University Hospital Na Bulovce- Department of Orthopaedic Surgery Postgraduate Medical Institute, Praha 9, Czech Republic, 180 81 |

ACI: autologous cartilage implantation
IKDC: International Knee Scoring Documentation Committee
ICRS: the International Cartilage Repair Society's cartilage injury evaluation package
KOOS: Knee Injury Osteoarthritis Outcome Score
MACI: matrix-guided autologous cartilage implantation
MRI: magnetic resonance imaging
VAS: visual analogue score

## DATA AND ANALYSES


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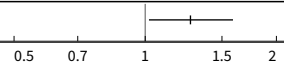
**Comparison 1. ACI versus mosaicplasty**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Good or excellent functional results (modified Cincinatti rating system) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2 Arthroscopic assessment at one year (ICRS grade 1 or 2) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3 Lysholm scores (0: worst to 100: best) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 3.1 at 6 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 at 12 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 at 24 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Tegner scores (0: worst to 10: best) at 24 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5 Meyers scores (higher scores better) at 24 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 6 Excellent outcome (various definitions) | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 6.1 Excellent (Cincinnatti score > 80; Lysholm score > 90) | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.2 Compete success - Lysholm score > 90 and symptom disappearance | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Satisfactory outcome (various criteria) - exploratory analysis | 3 | 177 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.81, 1.28] |

**Analysis 1.1. Comparison 1 ACI versus mosaicplasty, Outcome 1 Good or excellent functional results (modified Cincinatti rating system).**

| Study or subgroup | ACI n/N | Mosaicplasty n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| Bentley 2003 | 51/58 | 29/42 | | 1.27[1.02,1.59] |





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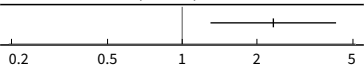
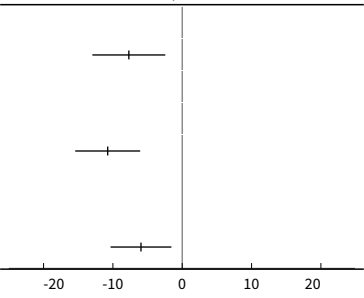
### Analysis 1.2. Comparison 1 ACI versus mosaicplasty, Outcome 2 Arthroscopic assessment at one year (ICRS grade 1 or 2).

| Study or subgroup | ACI n/N | Mosaicplasty n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| Bentley 2003 | 30/37 | 8/23 | | 2.33[1.3,4.17] |



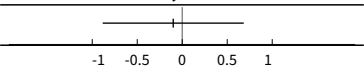

### Analysis 1.3. Comparison 1 ACI versus mosaicplasty, Outcome 3 Lysholm scores (0: worst to 100: best).

| Study or subgroup | ACI N | ACI Mean(SD) | Mosaicplasty N | Mosaicplasty Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **1.3.1 at 6 months** | | | | | | |
| Horas 2003 | 20 | 45.8 (10.1) | 20 | 53.5 (6.4) | | -7.7[-12.96,-2.44] |
| **1.3.2 at 12 months** | | | | | | |
| Horas 2003 | 20 | 57.5 (7.4) | 20 | 68.3 (7.7) | | -10.75[-15.43,-6.07] |
| **1.3.3 at 24 months** | | | | | | |
| Horas 2003 | 20 | 66.8 (8.3) | 20 | 72.7 (5.7) | | -5.95[-10.34,-1.56] |



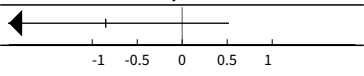

### Analysis 1.4. Comparison 1 ACI versus mosaicplasty, Outcome 4 Tegner scores (0: worst to 10: best) at 24 months.

| Study or subgroup | ACI N | ACI Mean(SD) | Mosaicplasty N | Mosaicplasty Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Horas 2003 | 20 | 5.1 (1.4) | 20 | 5.2 (1.1) | | -0.1[-0.88,0.68] |



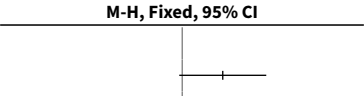

### Analysis 1.5. Comparison 1 ACI versus mosaicplasty, Outcome 5 Meyers scores (higher scores better) at 24 months.

| Study or subgroup | ACI N | ACI Mean(SD) | Mosaicplasty N | Mosaicplasty Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Horas 2003 | 20 | 15.9 (2.9) | 20 | 16.8 (1.2) | | -0.85[-2.22,0.52] |




### Analysis 1.6. Comparison 1 ACI versus mosaicplasty, Outcome 6 Excellent outcome (various definitions).

| Study or subgroup | ACI n/N | Mosaicplasty n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **1.6.1 Excellent (Cincinnatti score > 80; Lysholm score > 90)** | | | | |
| Bentley 2003 | 23/58 | 9/42 | | 1.85[0.96,3.58] |
| Dozin 2005 | 10/22 | 15/22 | | 0.67[0.39,1.14] |
| Horas 2003 | 0/20 | 0/20 | | Not estimable |





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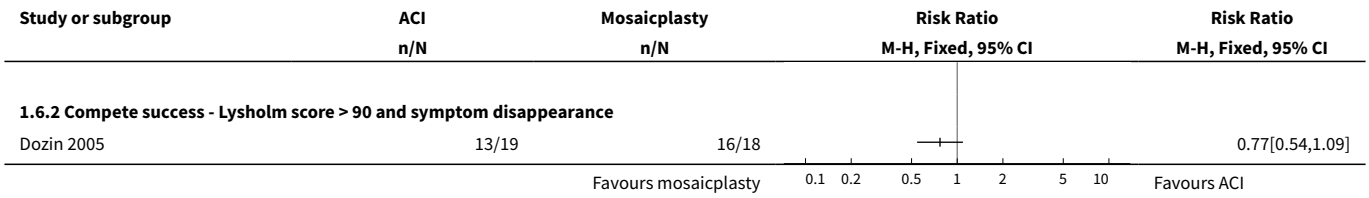
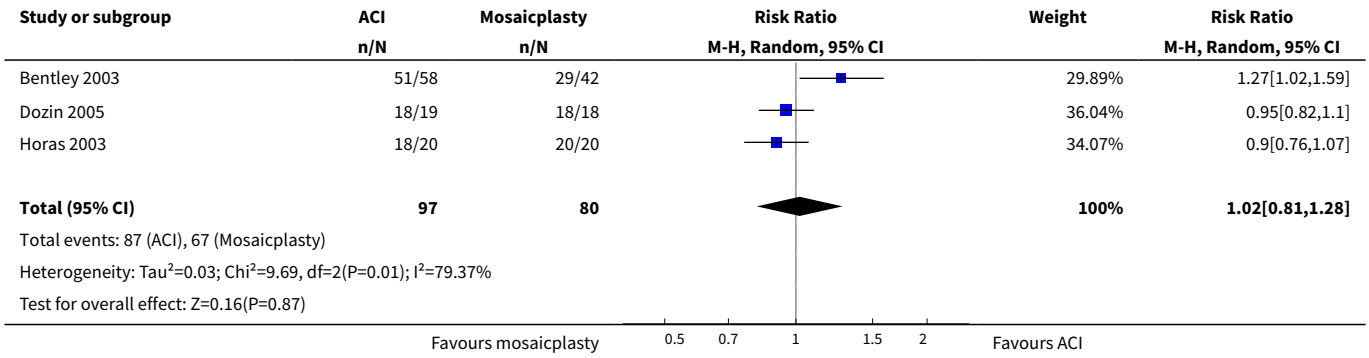


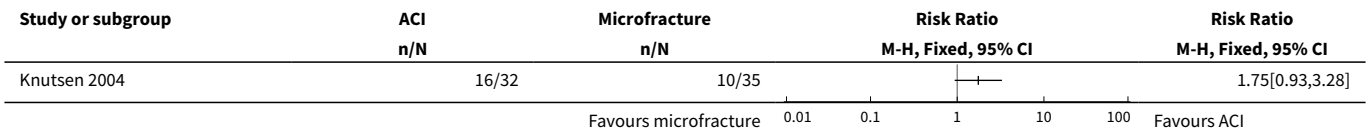

**Analysis 1.7. Comparison 1 ACI versus mosaicplasty, Outcome 7 Satisfactory outcome (various criteria) - exploratory analysis.**




## Comparison 2. ACI versus microfracture

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Presence of hyaline cartilage in biopsy | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2 Failure and further procedures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.1 "Failure" at 2 years | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Further procedures / arthroscopy | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 "Failure" at 5 years | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

**Analysis 2.1. Comparison 2 ACI versus microfracture, Outcome 1 Presence of hyaline cartilage in biopsy.**





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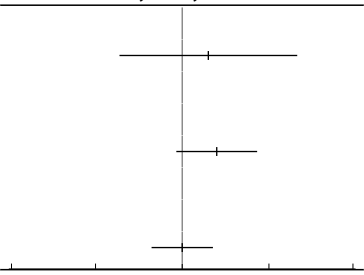
### Analysis 2.2. Comparison 2 ACI versus microfracture, Outcome 2 Failure and further procedures.

| Study or subgroup | ACI n/N | Microfracture n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **2.2.1 "Failure" at 2 years** | | | | |
| Knutsen 2004 | 2/40 | 1/40 | | 2[0.19,21.18] |
| **2.2.2 Further procedures / arthroscopy** | | | | |
| Knutsen 2004 | 10/40 | 4/40 | | 2.5[0.85,7.31] |
| **2.2.3 "Failure" at 5 years** | | | | |
| Knutsen 2004 | 9/40 | 9/40 | | 1[0.44,2.26] |

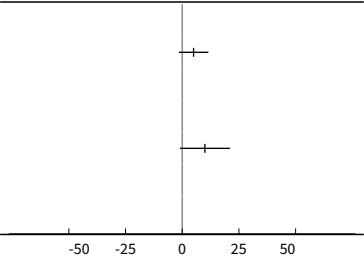



## Comparison 3. MACI versus microfracture

| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Lysholm scores (0: worst to 100: best) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 1.1 at 6 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 at 12 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 1.3 at 24 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Tegner scores (0: worst to 10: best) at 24 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 3 ICRS patient score (grade 1 or 2) at 24 months | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

### Analysis 3.1. Comparison 3 MACI versus microfracture, Outcome 1 Lysholm scores (0: worst to 100: best).

| Study or subgroup | MACI N | MACI Mean(SD) | Microfracture N | Microfracture Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.1.1 at 6 months** | | | | | | |
| Basad 2010 | 39 | 87 (17) | 88 | 82 (18) | | 5[-1.53,11.53] |
| **3.1.2 at 12 months** | | | | | | |
| Basad 2010 | 38 | 92 (11) | 17 | 82 (22) | | 10[-1.03,21.03] |
| **3.1.3 at 24 months** | | | | | | |





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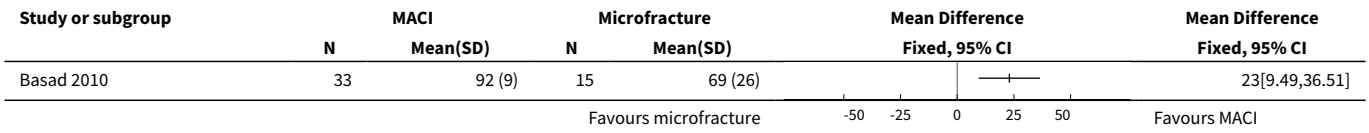
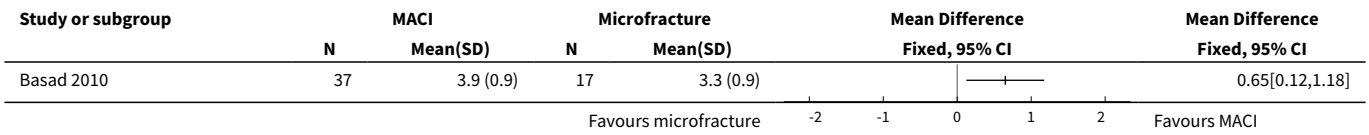
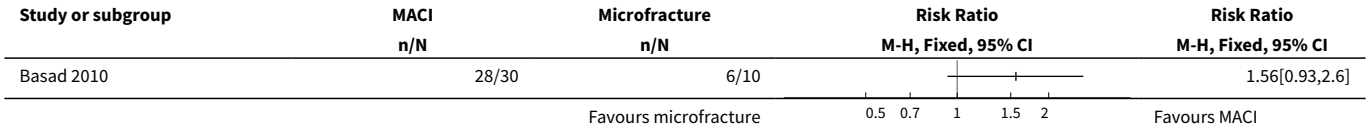



### Analysis 3.2. Comparison 3 MACI versus microfracture, Outcome 2 Tegner scores (0: worst to 10: best) at 24 months.




### Analysis 3.3. Comparison 3 MACI versus microfracture, Outcome 3 ICRS patient score (grade 1 or 2) at 24 months.




## Comparison 4. CCI (characterised chrondrocyte implantation) versus microfracture

| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Knee function up to 18 months (KOOS ("overall" minus 'sport' do-main): 0: extreme knee problems, 100: no knee problems) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 1.1 at 6 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 at 12 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 1.3 at 18 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 2 KOOS (improvement from baseline at 36 months) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 3 KOOS improvement from baseline at 36 months (adjusted data) | 1 | | Mean Difference (Fixed, 95% CI) | Totals not selected |
| 3.1 KOOS / overall (no sports domain) | 1 | | Mean Difference (Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 KOOS / ADL | 1 | | Mean Difference (Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 KOOS / pain | 1 | | Mean Difference (Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.4 KOOS / symptoms-stiffness | 1 | | Mean Difference (Fixed, 95% CI) | 0.0 [0.0, 0.0] |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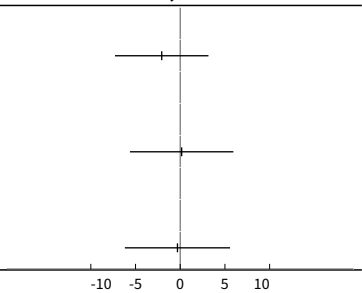
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.5 KOOS / QoL | 1 | | Mean Difference (Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.6 KOOS / sports | 1 | | Mean Difference (Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Treatment failure requiring re-intervention (up to 36 months) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 5 Adverse events (at 18 months) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 5.1 Treatment related adverse events | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 Treatment related 'serious' adverse events | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.3 Joint pain | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 Joint swelling | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.5 Joint crepitation | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Adverse events (at 36 months) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 6.1 Treatment related adverse events | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.2 Joint pain | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.3 Joint swelling | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.4 Joint crepitation | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

**Analysis 4.1. Comparison 4 CCI (characterised chrondrocyte implantation) versus microfracture, Outcome 1 Knee function up to 18 months (KOOS ("overall" minus 'sport' domain): 0: extreme knee problems, 100: no knee problems).**

| Study or subgroup | CCI N | CCI Mean(SD) | Microfracture N | Microfracture Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **4.1.1 at 6 months** | | | | | | |
| Saris 2008 | 51 | 70.6 (12.4) | 59 | 72.6 (15.6) | | -2.07[-7.3,3.16] |
| **4.1.2 at 12 months** | | | | | | |
| Saris 2008 | 51 | 73.3 (14.7) | 57 | 73.1 (16) | | 0.16[-5.62,5.94] |
| **4.1.3 at 18 months** | | | | | | |
| Saris 2008 | 44 | 74.7 (14.7) | 51 | 75 (14.5) | | -0.31[-6.19,5.57] |





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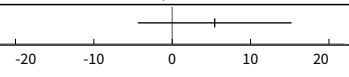
## Analysis 4.2. Comparison 4 CCI (characterised chrondrocyte implantation) versus microfracture, Outcome 2 KOOS (improvement from baseline at 36 months).

| Study or subgroup | CCI N | CCI Mean(SD) | Microfracture N | Microfracture Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Saris 2008 | 39 | 21.3 (22.5) | 43 | 15.8 (22.8) | | 5.42[-4.39,15.23] |



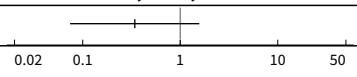

## Analysis 4.3. Comparison 4 CCI (characterised chrondrocyte implantation) versus microfracture, Outcome 3 KOOS improvement from baseline at 36 months (adjusted data).

| Study or subgroup | ACI N | other treatment N | Mean Difference (SE) | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|
| **4.3.1 KOOS / overall (no sports domain)** | | | | | |
| Saris 2008 | 44 | 51 | 7.7 (3.824) | | 7.66[0.16,15.15] |
| **4.3.2 KOOS / ADL** | | | | | |
| Saris 2008 | 44 | 50 | 6.4 (3.409) | | 6.4[-0.28,13.08] |
| **4.3.3 KOOS / pain** | | | | | |
| Saris 2008 | 44 | 51 | 7.3 (3.589) | | 7.33[0.3,14.37] |
| **4.3.4 KOOS / symptoms-stiffness** | | | | | |
| Saris 2008 | 44 | 51 | 5.8 (3.752) | | 5.84[-1.51,13.19] |
| **4.3.5 KOOS / QoL** | | | | | |
| Saris 2008 | 44 | 51 | 11.1 (5.221) | | 11.12[0.89,21.35] |
| **4.3.6 KOOS / sports** | | | | | |
| Saris 2008 | 44 | 51 | 10.8 (6.914) | | 10.82[-2.73,24.37] |




## Analysis 4.4. Comparison 4 CCI (characterised chrondrocyte implantation) versus microfracture, Outcome 4 Treatment failure requiring re-intervention (up to 36 months).

| Study or subgroup | CCI n/N | Microfracture n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| Saris 2008 | 2/51 | 7/61 | | 0.34[0.07,1.57] |




## Analysis 4.5. Comparison 4 CCI (characterised chrondrocyte implantation) versus microfracture, Outcome 5 Adverse events (at 18 months).

| Study or subgroup | CCI n/N | Microfracture n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **4.5.1 Treatment related adverse events** | | | | |



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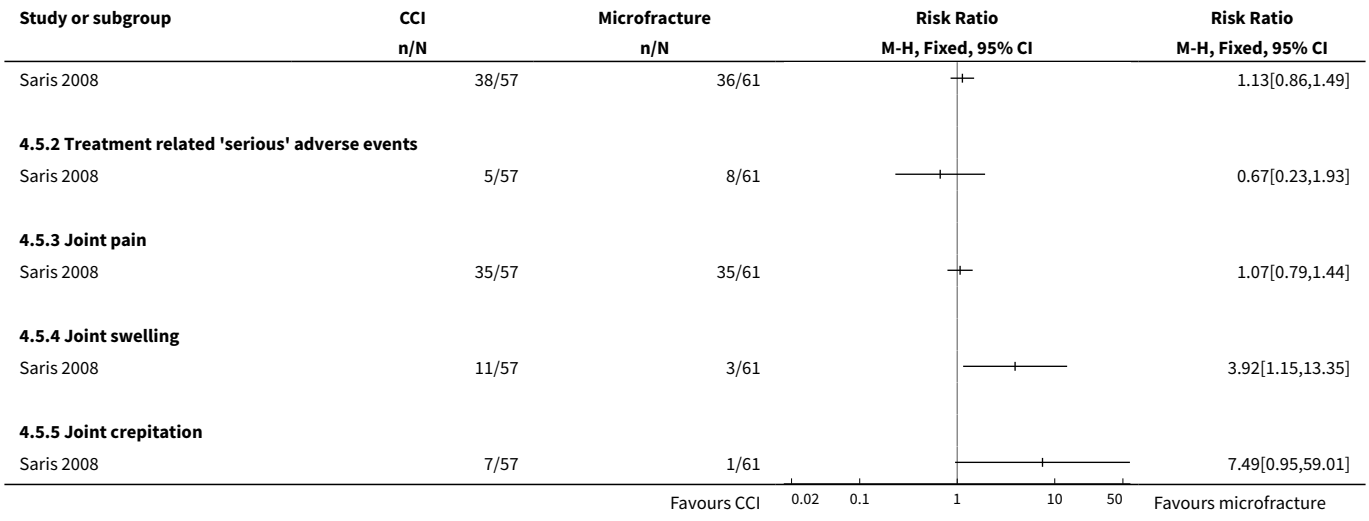
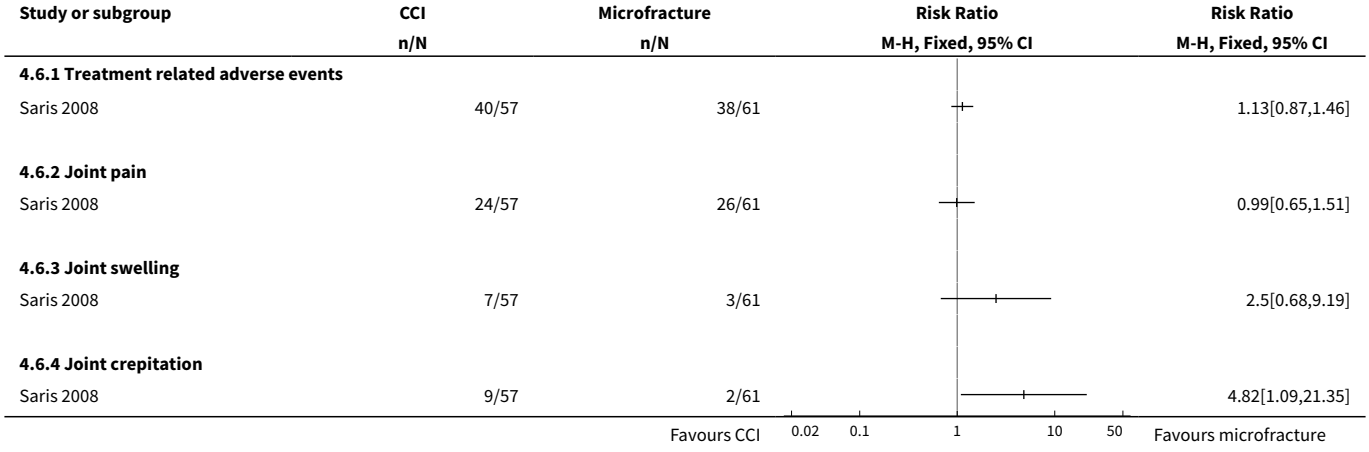



**Analysis 4.6. Comparison 4 CCI (characterised chrondrocyte implantation) versus microfracture, Outcome 6 Adverse events (at 36 months).**




# APPENDICES

## Appendix 1. Search strategies

### Cochrane Central Register of Controlled Trials (Wiley Online Library)

#1 MeSH descriptor Cartilage, Articular, this term only (150)
#2 MeSH descriptor Cartilage, this term only (56)
#3 MeSH descriptor Chondrocytes, this term only (37)
#4 (cartilage):ti,ab,kw (571)
#5 chondrocyte*:ti,ab,kw (64)
#6 (#1 OR #2 OR #3 OR #4 OR #5) (584)
#7 MeSH descriptor Knee, this term only (389)
#8 MeSH descriptor Knee Joint explode all trees (1487)
#9 MeSH descriptor Knee Injuries, this term only (390)
#10 MeSH descriptor Patella, this term only with qualifier: IN (20)
#11 ((medial or lateral) NEAR condyle*):ti,ab,kw (31)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#12 (trochlea*):ti,ab,kw (11)
#13 (patella*):ti,ab,kw (569)
#14 (knee):ti,ab,kw (6460)
#15 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) (6682)
#16 MeSH descriptor Transplantation, Autologous, this term only (879)
#17 (transplant*):ti,ab,kw (13859)
#18 MeSH descriptor Cell Transplantation, this term only (39)
#19 (implant*):ti,ab,kw (8486)
#20 ((autogen* or autolog*) NEAR (implant* or transplant*)):ti,ab,kw (1850)
#21 (#16 OR #17 OR #18 OR #19 OR #20) (21850)
#22 (#6 AND #15 AND #21) (39)

**MEDLINE (OvidSP)**

1. Cartilage, Articular/ (19247)
2. Cartilage/ (18989)
3. Chondrocytes/ (8437)
4. cartilage.tw. (46167)
5. chondrocyte$.tw. (15792)
6. or/1-5 (63092)
7. Knee/ (8880)
8. exp Knee Joint/ (34816)
9. Knee Injuries/ (12454)
10. Patella/in [Injuries] (1712)
11. ((medial or lateral) adj condyle$).tw. (688)
12. trochlea$.tw. (1851)
13. patella$.tw. (11090)
14. knee$.tw. (67892)
15. or/7-14 (89227)
16. Transplantation, Autologous/ (38480)
17. transplant$.tw. (266575)
18. Cell Transplantation/ (5635)
19. implant$.tw. (203934)
20. ((autogen$ or autolog$) adj (implant$ or transplant$)).tw. (2670)
21. tr.fs. (97522)
22. or/16-21 (537081)
23. and/6,15,22 (1770)
24. Randomized controlled trial.pt. (293680)
25. Controlled clinical trial.pt. (80582)
26. Randomized Controlled Trials/ (69038)
27. Random Allocation/ (69139)
28. Double Blind Method/ (106314)
29. Single Blind Method/ (14268)
30. or/24-29 (495792)
31. Animals/ not Humans/ (3394409)
32. 30 not 31 (459612)
33. clinical trial.pt. (453459)
34. exp Clinical Trials as topic/ (232165)
35. (clinic$ adj25 trial$).tw. (178314)
36. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw. (106849)
37. Placebos/ (28766)
38. placebo$.tw. (123750)
39. random$.tw. (491629)
40. Research Design/ (60208)
41. or/33-40 (1046042)


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42.41 not 31 (967346)
43.42 not 32 (541947)
44.or/32,43 (1001559)
45.23 and 44 (134)

**EMBASE (OvidSP)**

1. Articular Cartilage/ (16348)
2. Cartilage Injury/ or Cartilage/ or Cartilage Degeneration/ (29483)
3. Cartilage Cell/ (16097)
4. cartilage.tw. (52558)
5. chondrocyte$.tw. (18414)
6. or/1-5 (74810)
7. Knee/ (29154)
8. Knee Injury/ (9691)
9. patella/ (5896)
10. ((medial or lateral) adj condyle$).tw. (806)
11. trochlea$.tw. (2093)
12. patella$.tw. (13164)
13. knee$.tw. (83624)
14. or/7-13 (102007)
15. Autotransplantation/ (24200)
16. transplant$.tw. (317436)
17. Cell Transplantation/ (12671)
18. implant$.tw. (239327)
19. ((autogen$ or autolog$) adj (implant$ or transplant$)).tw. (3367)
20. tr.fs. (1737)
21. or/15-20 (564728)
22. and/6,14,21 (1595)
23. Clinical trial/ (824906)
24. Randomized controlled trial/ (287318)
25. Randomization/ (53237)
26. Single blind procedure/ (13723)
27. Double blind procedure/ (100818)
28. Crossover procedure/ (29926)
29. Placebo/ (172981)
30. Randomi?ed controlled trial$.tw. (58704)
31. Rct.tw. (6302)
32. Random allocation.tw. (1010)
33. Randomly allocated.tw. (15049)
34. Allocated randomly.tw. (1689)
35. (allocated adj2 random).tw. (680)
36. Single blind$.tw. (10645)
37. Double blind$.tw. (115284)
38. ((treble or triple) adj blind$).tw. (230)
39. Placebo$.tw. (153949)
40. Prospective study/ (161416)
41. or/23-40 (1111295)
42. Case study/ (10869)
43. Case report.tw. (195656)
44. Abstract report/ or letter/ (765754)
45. or/42-44 (968630)
46. 41 not 45 (1079070)


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47.limit 46 to human (993397)
48.22 and 47 (145)

**SPORTDiscus (Ebsco)**

S1 DE "ARTICULAR cartilage" (734)
S2 DE "CARTILAGE" (931)
S3 DE "CARTILAGE cells" (333)
S4 TX cartilage (2916)
S5 TX chondrocyte* (578)
S6 S5 or S4 or S3 or S2 or S1 (2971)
S7 DE "KNEE" (11261)
S8 DE "PATELLA" (1553)
S9 TX medial N6 condyle* or TX lateral N6 condyle (366)
S10 TX trochlea* (199)
S11 TX patella* (3716)
S12 TX knee* (28176)
S13 S12 or S11 or S10 or S9 or S8 or S7 (29378)
S14 DE "AUTOTRANSPLANTATION" (254)
S15 TX transplant* (2575)
S16 TX implant* (8707)
S17 TX autogen* N6 implant* or TX autogen* N6 transplant* or TX autolog* N6 implant* or TX autolog* N6 transplant* (287)
S18 S17 or S16 or S15 or S14 (11107)
S19 S18 and S13 and S6 (436)
S20 TX ((clinic$ or controlled or comparative or placebo or prospective or randomised or randomized) and (trial or study)) (56886)
S21 TX (random* and (allocat* or allot* or assign* or basis* or divid* or order*)) (8277)
S22 TX ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) (4103)
S23 TX (cross?over or (cross over) (710)
S24 TX randomi?ed control* trial* (3737)
S25 TX ((allocat* or allot* or assign* or divid*) and (condition* or experiment* or intervention* or treatment* or therap* or control* or group*)) (13589)
S26 TX placebo* (5828)
S27 S26 or S25 or S24 or S23 or S22 or S21 or S20 (69428)
S28 S27 and S19 (118)

**WHO International Clinical Trials Registry Platform**

1. cartilage AND autologous
2. cartilage AND autogenous
3. cartilage AND knee AND transplant*
4. cartilage AND knee AND implant*
5. chondrocyte AND autologous
6. chondrocyte AND autogenous
7. cartilage AND knee AND transplant*
8. cartilage AND knee AND implant*

**Current Controlled Trials**

1. cartilage AND autologous
2. cartilage AND autogenous
3. cartilage AND knee AND transplant%
4. cartilage AND knee AND implant%
5. chondrocyte AND autologous
6. chondrocyte AND autogenous
7. cartilage AND knee AND transplant%
8. cartilage AND knee AND implant%

## WHAT'S NEW


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| Date | Event | Description |
|---|---|---|
| 13 May 2011 | New search has been performed | In this update (Issue 7, 2011), the following changes were made:<br>1. The search was updated to January 2011.<br>2. A trial report (Basad 2010) for an already included trial (Basad 2004) was taken to be the first definitive account of this trial.<br>3. A longer term follow-up (Saris 2009) of an already included trial (Saris 2008) was included. Additionally, two reports (Van Assche 2009; Van Assche 2010) reporting results for a subgroup of trial participants of Saris 2008 were included.<br>4. New data from the newly included trial reports were added to the 'Data and Analysis' section and Results. |

## HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 4, 2002

| Date | Event | Description |
|---|---|---|
| 3 September 2010 | New search has been performed | In this update, (published Issue 10, 2010), the following changes were made:<br>1. The title was changed from 'Autologous cartilage implantation for full thickness articular cartilage defects of the knee'.<br>2. The search was updated to December 2008. Two new trials were included (Dozin 2005; Saris 2008); as well as a long-term follow-up report for an already included trial (Knutsen 2004).<br>3. Risk of bias assessment was undertaken and the review was reformatted. |
| 3 September 2010 | New citation required but conclusions have not changed | There were changes in the authorship. |
| 4 September 2008 | Amended | Converted to new review format. |
| 17 May 2006 | New citation required but conclusions have not changed | In this substantive update, (published Issue 3, 2006), the following changes have been made:<br>1. The search was updated to December 2005.<br>2. Four new studies were included (Basad 2004; Bentley 2003; Horas 2003; Knutsen 2004).<br>3. Three studies were excluded (Bartlett 2005; Bickerstaff 2005; Schneider 2003).<br>4. Data from the four studies comparing ACI versus any other type of treatment (including no treatment or placebo) could not be pooled and are described individually.<br>5. The 'Conclusions' have been revised. |

## CONTRIBUTIONS OF AUTHORS

Haris Vasiliadis (HV): background, literature searching, study selection, review development, drafting of written submissions.

Jason Wasiak (JW): conception of revision, background, literature searching, study selection, review development, drafting of written submissions.


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## DECLARATIONS OF INTEREST

None known.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We clarified in Types of participants that cartilage defects should be "isolated".

We addressed the 'Risk of bias' tool as described by Higgins 2006, rather than the Schulz 1995 criteria, according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Cartilage, Articular [*surgery]; Chondrocytes [*transplantation]; Knee Injuries [*surgery]; Orthopedic Procedures [methods]; Randomized Controlled Trials as Topic; Transplantation, Autologous

### MeSH check words

Humans


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