Osteoarthritis and Cartilage 18 (2010) 857–863

Osteoarthritis and Cartilage

Effectiveness of autologous chondrocyte implantation in cartilage repair of the knee: a systematic review of controlled trials

P. Vavken †*, D. Samartzis ‡

† Department of Orthopedic Surgery, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA
‡ Department of Orthopaedics and Traumatology, Queen Mary Hospital, University of Hong Kong, Pokfulam, Hong Kong, China

ARTICLE INFO

Article history:
Received 18 September 2009
Accepted 4 March 2010

Keywords:
Autologous chondrocyte implantation
Cartilage repair
Evidence-based medicine
Systematic review
Outcome assessment

SUMMARY

Objective: The relative differences in effectiveness of subchondral stimulation, osteochondral grafts, and autologous chondrocyte implantation (ACI) are still unclear. It is the objective of this study to systematically review the literature on ACI compared to other treatments by clinical outcome and the quality of the repair tissue, including an assessment of the validity of these findings.
Method: The online databases PubMed, EMBASE, Cochrane Controlled Trial Register, CENTRAL, CINAHL, and BioMed were searched. Controlled trials comparing ACI with other methods of cartilage repair or placebo were included. Data on clinical outcome and the quality of the repair tissue was abstracted in duplicate. Study validity was assessed by individual components (randomization, blinded outcome assessment, sample size, attrition, percentage biopsies).
Results: Nine studies were included. The internal validity of most of these studies was poor. Studies comparing ACI with subchondral stimulation have a higher quality and show no differences in clinical outcomes, but suggest better results in tissue quality. The high quality evidence comparing ACI with osteochondral grafts shows better clinical outcomes and higher tissue quality after ACI.
Conclusion: Among the included studies there is much inconsistency in methodological quality and findings. Regardless of these problems, the absolute differences between groups are fairly small, thus raising questions about their clinical importance. Future studies will be needed to answer the question of benefits of ACI compared to other treatments, and could profit from addressing and avoiding the problems seen in this group. Finally conclusions concerning long-term effects are still difficult.

Introduction

Recently, biological regeneration has become popular in patient management in osteoarthritis, primarily to account for the ever-growing population of younger and more active patients. Current estimates of the prevalence of focal cartilage defects of the knee range from 5% to 11% in young patients and up to 60% in older patients[1–3]. Gerber *et al.*[4] followed 1321 patients with joint injuries over 36 years on average and found 13.9% progressed to fully developed knee osteoarthritis by the age of 65, with a significant 5.2 fold increase in risk compared to controls. Although there is considerable variation in the time interval between the occurrence of focal cartilage defects and the onset of osteoarthritis, there is a large proportion of younger patients suffering from cartilage defects and likely to develop osteoarthritis. Due to their young age and unabated demand for high mobility, these patients do not respond optimally to total joint replacement. Biological repair is the most valuable option to address the needs of this population. Two parameters describe the success of such procedures: the immediate clinical effect and the quality of the repair tissue as a predictor of the longevity of results.

The available options in biological repair for cartilage defects of the knee are (1) subchondral marrow stimulation[5,6], (2) osteochondral graft transfer[7], and (3) autologous chondrocyte implantation (ACI)[8]. Among these, ACI is technically most advanced and holds much promise for true healing rather than fibrous scarring; however, such assumptions warrant robust evidence. A number of randomized controlled trials have been conducted to compare ACI with the abovementioned other options in cartilage repair, but have shown fairly inconsistent results[9]. Furthermore, both the design and conduct of some of these trials have been criticized and the

* Address correspondence and reprint requests to: P. Vavken, Department of Orthopedic Surgery, Children's Hospital Boston, Harvard Medical School, 300 Longwood Avenue, Enders 1016, Boston, MA 02115, USA. Tel: 1-617-919-2105; Fax: 1-617-730-0170.
E-mail address: Patrick.vaken@childrens.harvard.edu (P. Vavken).

1063-4584/$ – see front matter © 2010 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.joca.2010.03.005

validity of their findings has been questioned[10]. However, recently, various randomized controlled trials with sufficiently long follow-up were published[11,12]. Some of these trials were pooled in a recent systematic review, but only clinical outcome, not quality of repair tissue or study validity, was considered[13].

In an effort to further assess the evidence of options in cartilage repair of the knee, our study was multifaceted. Our first objective was to address a systematic review of the evidence for the short- and long-term efficacy of ACI compared to subchondral marrow stimulation and osteochondral graft transfer, as measured by clinical effect and repair tissue quality. The second objective was to assess the quality of published trials and in a comparative context to the validity of the findings presented in the existing literature.

Methods

Search strategy

Online searches of the databases PubMed, EMBASE, Cochrane Controlled Trial Register, CENTRAL, CINAHL, and BioMed were performed. Briefly, the terms "autologous chondrocyte implantation", "autologous chondrocyte transplantation" and "knee" were combined without restrictions concerning language or date of publication. See the Appendix for full description of the search algorithms. These results were searched for controlled trials using a highly sensitive and validated filter, and reviewed by hand for eligible studies[14,15]. The bibliographies of relevant papers were searched for further studies. All searches were concluded by December 2009.

Study selection

All controlled trials comparing ACI with another treatment or placebo in humans with a minimal follow-up of 6 months were eligible for inclusion. Studies were included if the treatment group received ACI of any type for a cartilage defect in the knee compared to a group receiving another cartilage repair procedure or placebo. Procedures addressing the pathogenesis of the cartilage defect in individual patients, such as malalignment or instability, were not considered exclusion criteria. Case reports, case series, retrospective studies, non-randomized controlled trials, and studies systematically focusing on the combined efficacy of ACI and other major procedures, such as meniscus replacement, were excluded from further review.

Data abstraction

Data were abstracted for the endpoints clinical outcome, reported in any form at 1 year of follow-up and at the latest follow-up, and quality of repair tissue (in arthroscopic and histological assessment and as description of failures). Also, parameters pertinent for validity assessment and demographics of the studied populations were abstracted. All data were independently extracted twice and cross-checked for errors.

Validity assessment

Level-of-evidence was determined for all included studies (as given on www.ejbjs.org). Internal validity was assessed by the following components: appropriateness of randomization procedure (yes/no), blinding of outcome assessment (yes/no), *a priori* sample size calculation (yes/no), attrition reported and accounted for in analysis (yes/no), and percentage of biopsies. Appropriate randomization was defined as computer-generated sequences or random number tables, with concealed allocation *via* opaque envelopes or an independent referee, or equivalent methods. Alternating allocation, allocation based on date, or other predictable methods were considered inappropriate. The use of composite validity scales was avoided, since this has been shown to be problematic[16].

Results

Study characteristics

Our literature search produced 367 papers in online databases and one in hand searches. After exclusion of duplicates 238 were reviewed for eligibility. Seven level-I (high quality) and −II (low quality, i.e., <80% follow-up, improper randomization, no blinding) randomized controlled trials, published in 10 papers, were included[11,12,17–24]. A subgroup from one of the included trials[12] was published independently[25], but this paper was not included since outcomes for the whole population are given in the first publication[12]. Details of search results are illustrated in Fig. 1. All included studies were published between 2000 and 2008 in English or German and compared different subtypes of ACI with osteochondral allografts ($n = 4$) or subchondral marrow stimulation ($n = 5$) in a total of 526 patients (Table I).

Clinical outcome

Comparing ACI with microfracture Saris *et al.* found no difference in KOOS scores, based on a minimal difference of 9% between 95% CI at 24 months, but significantly better outcomes for ACI at 36 months. Knutsen *et al.* found no significant difference in functional scores at 2 or 5 years either, but a significantly better result in the physical component of the SF-36 for microfracture. Basad found better results for ACI compared with microfracture on the Meyers, Lysholm, Tegner, and ICRS score, but presents no statistical inference with his preliminary results. Visna *et al.*, comparing

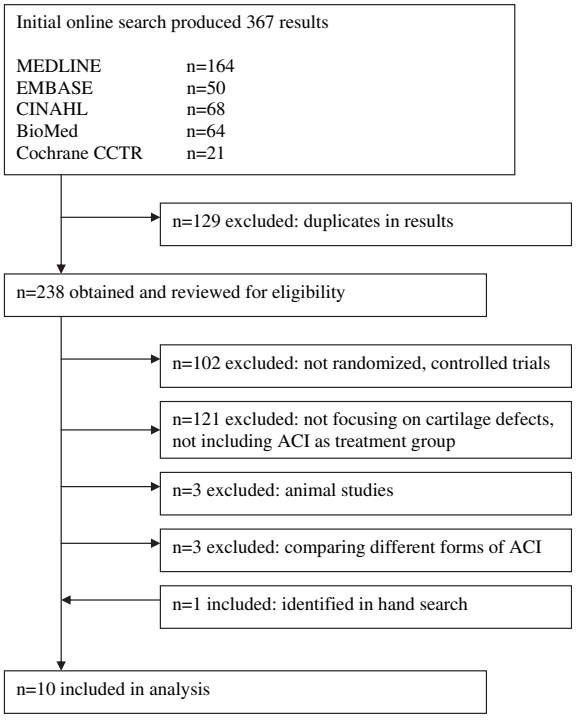

Fig. 1. Trial flow.

Table I
Characteristics of included studies

Author	Year	*n* (ACI/control)	Controls treated with	Reported outcomes	Last follow-up at (months)	Average defect size (cm^2, ACI/control)	Gender ratio (m/f)
Horas *et al.*[21]	2000	40 (20/20)	Osteochondral autograft transfer	Subjective outcome, Lysholm, Tegner, Meyer, MRI, histology, IHC, electron microscopy	24	4.4	23/17
Horas *et al.*[20]	2003	40 (20/20)	Osteochondral autograft transfer	Lysholm, Tegner, Meyer, histology, IHC	24	3.9/3.6	23/17
Bentley *et al.*[17]	2003	100 (58/42)	Osteochondral autograft transfer	Modified Cincinnati and Stanmore, histology	19	4.66	57/43
Dozin *et al.*[19]	2005	34 (22/22)	Osteochondral autograft transfer	Lysholm, IKDC	25	2.0/1.9	27/17
Knutsen *et al.*[22]	2004	80 (40/40)	Microfracture	Lysholm, SF-36, Tegner score, ICRS, histology	24	5.1/4.5	48/32
Knutsen *et al.*[11]	2007	80 (40/40)	Microfracture	ICRS, Lysholm, SF-36, Tegner	60	5.1/4.5	48/32
Basad *et al.*[24]	2004	19 (10/9)	Microfracture	Meyers, Lysholm, Tegner, ICRS	12	3.8/4.2	–
Saris *et al.*[23]	2008	118 (57/61)	Microfracture	Histology, KOOS, safety	18	2.6/2.4	76/42
Saris *et al.*[12]	2009	85 (41/44)	Microfracture	MRI (MOCART), KOOS, safety	36	2.6/2.4	–
Visna *et al.*[18]	2004	50 (25/25)	Abrasion	Lysholm, IKDC, Tegner, ICRS, histology	12	4.1/3.4	34/16

subchondral abrasion with ACI, found significantly better results in Lysholm, IKDC, and Tegner scores for patients treated with ACI at 12 months.

Bentley *et al.* compared ACI with osteochondral grafts and found no difference in combined good and excellent results, although there were 23 excellent results with ACI and only nine with OAT at 19 months on average. Horas *et al.*, too, compared ACI with osteochondral grafting, and found no significant difference in outcomes on clinical scores at 2 years, but reported on a slower increase in scores with ACI. Dozin *et al.*, in his study troubled by patient compliance and attrition, found no significant differences in clinical outcome, either. Clinical outcome is summarized in Table II.

Quality of repair tissue

The quality of repair tissue was assessed arthroscopically in six studies, using the ICRS score or descriptive assessment[26]. A systematically performed morphological assessment during second look arthroscopies was done by Bentley *et al.* and Knutsen *et al.* to compare ACI with osteochondral grafts or microfracture in 60% and 84% of their patients, respectively. While Knutsen *et al.* observed no difference in ICRS scores for ACI and microfracture at 2 years, Bentley *et al.* saw a significantly better result after ACI at 1 year. Horas *et al.* reported on second look arthroscopies in six ACI cases and three OAT cases after a maximum follow-up of 21 months (23% of all included patients), but did not see differences in repair tissue. However, he found persistent gaps around the graft, an observation supported by Bentley *et al.* Visna *et al.* followed four patients from his ACI group arthroscopically and found two sufficiently healed defects and two failures.

A systematic, comparative, histological assessment of biopsies was done by Saris *et al.* and Knutsen *et al.* for ACI compared with microfracture, and by Bentley *et al.* comparing ACI with osteochondral grafts. Saris *et al.* found significantly better results after ACI. Knutsen *et al.* found no significant difference in the frequency of hyaline-like repair tissue after ACI or microfracture, although there seems to be at least a borderline significance at $P = 0.08$. More importantly there was no association between histology and clinical outcome at 2– and 5 years. However, there was a significant association between poor macroscopic outcome and the likelihood of failure, and an unclear association between failures and poor histology. Bentley *et al.*, in turn, found a significant superiority of ACI over osteochondral grafting in histological analysis. Horas *et al.* reported no differences in histological, immunohistochemical, and electron-microscopic analyses of patients after ACI and osteochondral grafting, but only in a rather small proportion of cases (23%). Histological outcomes are summarized in Table II.

Table II
Clinical and histological outcomes among included studies

ACI vs	Author	Year	Clinical outcome	Histological outcome	Conclusion
Osteochondral autograft transfer	Horas *et al.*[21]	2000	No differences in clinical scores	Fibrocartilaginous defect filling in ACI, no visible changes in tissue after OAT	Prefer OAT over ACI
	Horas *et al.*[20]	2003	No differences in clinical scores	Fibrocartilaginous defect filling in ACI, no visible changes in tissue after OAT	Prefer OAT over ACI
	Bentley *et al.*[17]	2003	88% good and excellent after ACI, 69% after OAT	82% good and excellent after ACI, 34% after OAT	"…a significant superiority of ACI over mosaciplasty… "
	Dozin *et al.*[19]	2005	Complete recovery in 68% after ACI, 88% after OAT	No histology	"…although low power… ACI and mosaicplasty are… clinically equivalent…"
Microfracture	Basad *et al.*[24]	2004	ACI had better results in clinical scores	No histology	"good and very good clinical results… only a temporary assessment…"
	Knutsen *et al.*[22]	2004	No differences in Lysholm scores, MFX better in SF-36	No difference, no association with clinical outcome	"…Mid-term and long-term follow-up is needed to determine if one method is better…"
	Knutsen *et al.*[11]	2007	No differences in scores, no more difference in SF-36	No histology	"…no significant difference in the clinical and radiographic results…"
	Saris *et al.*[23]	2008	No difference	Better results for ACI	"…tissue regenerate that was superior to that after microfracture…"
	Saris *et al.*[12]	2009	Improvement after ACI better than MFX	No histology	"ACI … results in significantly better clinical outcome after 36 months…"
Abrasion	Visna *et al.*[18]	2004	ACI superior	No histology	"…better outcome in patients treated with ACI…"

MRI assessment revealed no difference in repair tissue between ACI and microfracture after 36 months, although there was more subchondral plate elevation in microfractured patients. Horas reported bone marrow edema on MRI persisting for 12 months after ACI and mosaicplasty. By 24 months in ACI patients the edema had resolved and the defect showed a homogenous repair tissue, yet with T2 hyperintensity. Twenty-four months after mosaicplasty Horas reported irregular signaling at the osseous interfaces and hypointense T1 signals for the bone plug.

For microfracture vs ACI, Knusten reported nine failures each after 5 years of follow-up. In his study, 25% of the ACI cases underwent debridement compared to 10% of the microfractured patient. Saris reported similar numbers with 25% of his ACI cases developing cartilage hypertrophy compared to 13% of the microfractured cases. Overall, Saris *et al.* observed 67% and 59% adverse events in ACI and microfracture, respectively, but only 9% and 13% serious events for ACI and microfracture. For mosaicplasty, Bentley *et al.* reported four failed treatments in which the plugs were *in situ* but no tissue had formed in between and three cases in which the plugs had disintegrated. Horas reported to have seen gaps between the plugs and adjacent cartilage in all second look arthroscopies.

Validity assessment

Assessment of study validity revealed rather insufficient results for most studies. Detailed results are given in Table III. Briefly, there is reason to question the internal validity of the findings in most studies. Power analyses and sample size calculations were not done in five out of nine studies, and sample size was not adjusted for multiple testing in any, although up to eight endpoints were analyzed in parallel. Randomization was adequate in most studies, except in the two studies by Horas *et al.*, who allocated patient alternately in order of presentation, thus in a highly predictable manner. Allocation concealment was insecure in all studies, and successful blinding of patients is unlikely, since ACI requires a second operation and OAT or microfracture do not. Also, while microfracture and osteochondral grafting is performed arthroscopically, ACI is an open procedure leaving a scar, thus making concealment of allocation during clinical examination difficult. Horas *et al.* report that all their patients were informed about their allocation status and offered the option to change their allocation. These facts strongly suggest a potential for considerable bias. Histological outcome assessment was reportedly blinded in most cases, but it often remained unclear whether clinical outcome assessment was blinded, too. Attrition rates for clinical outcome assessment were fairly, if not surprisingly, low in most studies, but in the paper published by Dozin *et al.* Most alarmingly, however, were attrition rates in arthroscopic and histological assessment, the secondary outcomes of this study and the main variables for prediction of long-term outcomes. Also, these facts suggest that there might be severe bias insofar as patients with beneficial outcomes did not present for follow-up, and only those with poor outcomes answered to the invitation for follow-up and were included in the analysis. Among those studies reporting analyses of histological data, only one study included at least 80% of patients for such assessment[22], and only three studies included more than half of their patients[17,22,23].

Discussion

It was the objective of this review to assess the current evidence for the efficacy of ACI compared to other methods of cartilage repair. As a second objective, we wanted to analyze the validity of the included studies and their findings, to make sure our interpretations are accurate. Given the substantial heterogeneity among the included studies it is not sensible to perform a quantitative data analysis to present a meta-analysis of the data.

In direct comparison of clinical outcomes there seems to be valid and reliable evidence for equivalent outcomes after ACI and microfracture in the short-term, based on the high-quality studies by Knutsen and Saris. Concerning osteochondral grafting, Bentley presented strong evidence for a higher efficacy of ACI. Finally, Gudas *et al.* presented findings suggesting that mosaicplasty has better outcomes than microfracture[27]. However, problems in the clinical assessment are the rather short follow-up periods, and, maybe more importantly, the choices of instruments. Sackett pointed out the necessity to use validated questionnaires specific for the condition being studied[28]. Hambley *et al.* and Tanner *et al.* studied the reliability of different scores for articular cartilage repair and reported that primarily the IKDC and secondly the KOOS give the most accurate description of symptoms and disabilities experienced by patients[29,30]. The ICRS score, too, was specifically designed and validated to study cartilage injuries and repair[26]. The Lysholm score has been shown to be valid for chondral defect treatment after modification and with some exceptions[31,32]. The reported Meyers, and modified Cincinnati scores still await validation for ACI. Thus, only six out of nine studies reported on cartilage-specific scores, and only four used a validated instrument. This runs in parallel to the question whether follow-ups were sufficiently long for valid clinical assessment or definitive conclusions about tissue differentiation. It has been shown that outcome after ACI improves significantly over the first 2 years, and that there is still some improvement during the third postoperative year[33]. Only Knutsen reported on results at more than 2 years, although both Basad and Horas planned to so[11,21]. Also, it has been shown that the outcome in patients undergoing microfracture deteriorates from 18 to 36 months, suggesting failure of the repair tissue[34].

There seems to be a general trend for higher quality of repair tissue after ACI, suggesting better long-term results when compared to microfracture and osteochondral grafts. There are two reasons for better results after ACI: first of all the capacity of ACI to create hyaline cartilage, and secondly problems associated with the

Table III
Quality parameters of included studies

Author	Year	Sample size	Randomization procedure	Blinding of assessors	Attrition	% With biopsies	Level-of-evidence†
Horas *et al.*[21]	2000	No	Alternating consecutive	Histology	5%	20%	II
Horas *et al.*[20]	2003	No	Alternating consecutive	Histology	5%	20%	II
Bentley *et al.*[17]	2003	No	Not specified	Unclear	0%	60%	II
Dozin *et al.*[19]	2005	Yes	Coordinating center	Surgeon assessed outcomes	15.9% (26.75)*	No Bx	II
Knutsen *et al.*[22]	2004	Yes	Sealed envelopes	Histology and clinical	0%	84%	I
Knutsen *et al.*[11]	2004	No	Not specified	Surgeon assessed all	0%	No Bx	I
Basad *et al.*[24]	2007	Yes	Sealed envelopes	Primary investigator assessed all	0%	No Bx	I
Saris *et al.*[23]	2008	Yes	Minimization	Histology, clinically self-assessed	17%	73%	I
Saris *et al.*[12]	2009	Yes	Minimization	MRI, clinically self-assessed	28%	No Bx	II
Visna *et al.*[18]	2004	No	Sealed envelopes	Not specified	0%	8%	II

* Of required sample size.
† As delineated by JBJS-A.

other procedures, such as intralesional osteophytes after microfracture (up to 27–33% incidence in MRI follow-up studies)[5,34,35] and persistent gaps between osteochondral grafts and the adjacent cartilage[17,20]. However, there are some potential problems associated with prediction of long-term outcome based on histological assessment, since the selection of individuals for such analysis was problematic at best in most of the included studies. Although it is understandable that investigators, surgeons, have compunction about jeopardizing outcomes by taking biopsies and thus disrupting the treasured repair tissue, but this must not lead to assessing only those patients in need of reoperation because of treatment failures. Yet it seems this happened quite frequently, as only one study assessed at least 80% of participants. Finally, Knutsen quite unexpectedly found no association between histological findings at 2 years and clinical outcome at 5 years, although he did find a significant association between macroscopic quality and likelihood of failure[11]. These findings suggest that a high quality repair cannot guarantee excellent clinical outcome, but that poor quality tissue will lead to clinical failure. This interpretation is supported by results presented by Henderson and colleagues, who were able to show that hyaline repair tissue had better outcomes in biomechanical testing, whereas fibrocartilaginous repair was associated with persisting symptoms in the affected joint[36]. In future studies it might be reasonable to use MRI, a non-invasive, non-destructive instrument that has been shown to be capable of monitoring cartilage maturation, to supplement or even replace histological outcome assessment[37–39].

One important point in systematically reviewing evidence is the validity of the included findings. The rather low overall methodological quality of most cartilage repair studies, and their propensity to bias, has been documented before[10]. This poses a direct threat to our study, thus we studied the validity of the included studies explicitly. From what has been reported it seems that there are significant differences in patient populations concerning defect size and specifics of treatment, raising questions about selection bias and external validity of the reported findings. Defect sizes are of particular concern, since there is considerable variation, and small defects are known to respond favorably to almost any treatment or might even become asymptomatic without treatment – as has been seen by Dozin[19]. Furthermore, high attrition rates, often insufficient randomization, and uncertainty about blinding of observers engender concerns about internal validity. In addition to high attrition rates, only four studies report on sample size calculations, and none adjusted for multiple testing, raising further questions concerning power. However, it should not go unnoticed that these observations build only on what has been reported, which is not necessarily the same as what has been done[40]. Finally, during the time in which the included studies were performed, the ACI technique evolved considerably. Not only were biomaterials introduced into the field, eliminating such complications as hypertrophy while reducing the technical complexity of the procedure[41], but surgeons also increased their understanding of the multi-factorial nature of cartilage defects. Once such problems as instability and malalignment were addressed appropriately, even "impossible locations" such as patellar defects could be successfully treated with ACI[42,43]. These developments are only inadequately reflected in the existing randomized controlled trials. However, these developments have also led us to put thought into the notion how much of the reported improvement is afforded by to the actual cartilage repair, and how much due to "ancillary measures". In summary, these flaws might very well have caused serious bias in the current cartilage repair literature, the size of which unfortunately cannot be estimated. Future studies should consider these facts and avoid such flaws in their design phase.

Previous studies reviewed the evidence for ACI or cartilage repair, but without coming to definitive conclusions[9,44–46]. However, this study encompasses more primary trials than any other thus far published, also because it included non-English language studies too. However, there are some shortcomings associated with this study. Despite a comprehensive search strategy, relevant studies might have been overseen, but given the popularity of ACI this seems unlikely. Also, as mentioned above, all interpretations presented in this study derive from published information, and important details concerning study design might have been omitted for the sake of publication length, or because they were deemed not interesting enough for presentation to an orthopedic audience. It should also be noticed that in this field of medicine it is difficult to follow study design recommendations, since double-blinding is nearly impossible unless all patients undergo two operations, which is ethically difficult. Also ACI can hardly be seen as one, standardized treatment, due to technical differences, and inter-patient variation in cell quality. This fact has been addressed by Saris and Basad by imposing strict quality controls on their *in-vitro* cell processing units[23,24]. Beyond control, however, is the patients biological response to implanted cells.

Conclusion

In conclusion, no clear recommendation concerning the efficacy of ACI compared to the treatment options microfracture or osteochondral grafts can be deducted from the existing literature. There is some evidence for better clinical outcomes for ACI compared with osteochondral grafts and equivalent outcomes compared with microfracture in those studies with high internal validity. Additionally and in combination with other studies on microfracture, it seems that there truly is evidence for a higher quality in repair tissue after ACI than with other procedures, and there is reason to believe that this high quality will be relevant for improving the longevity of effects. It is important to note that the absolute differences between treatment groups, regardless of significance, are mostly rather small, thus raising the question of clinical importance beyond mere statistical significance.

Conflict of interest

No funding was obtained for this study. Both authors have no conflict of interest.

Appendix. Search algorithm

PubMed Search

#1 Search "autologous chondrocyte implantation"
#2 Search "autologous chondrocyte transplantation"
#3 Search "knee"
#4 Search #1 or #2
#5 Search #3 and #4
#6 Search (((randomized controlled trial) OR (controlled clinical trial) OR (randomized controlled trial[mh]) OR (random allocation[mh]) OR (double-blind[mh]) OR (single-blind[mh])) NOT (animal[mh] NOT human[mh])) OR (((clinical trial) OR (clinical trials[mh]) OR ("clinical trial"[tw]) OR ((("singl*"[tw]) OR ("doubl*"[tw]) OR ("treb*"[tw]) OR ("tripl*"[tw])) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR (placebos[mh]) OR (placebo*[tw]) OR (random*[tw]) OR (research design[mh:noexp])) NOT (animal[mh] NOT human[mh])) OR ((((comparative study[mh]) OR (evaluation studies[mh]) OR (evaluation studies[mh]) OR (follow-up studies[mh]) OR (prospective studies[mh]) OR (cross-over studies[mh]) OR (control*[tw]) OR (prospectiv*[tw]) OR (volunteer*[tw])) NOT (animal[mh] NOT human[mh])) NOT ((((clinical trial) OR (clinical trials[mh]) OR ("clinical trial"[tw]) OR ((("singl*"[tw])

OR ("doubl*"[tw]) OR ("treb*"[tw]) OR ("tripl*"[tw])) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR (placebos[mh]) OR (placebo*[tw]) OR (random*[tw]) OR (research design[mh:noexp])) NOT (animal[mh] NOT human [mh])) OR (((randomized controlled trial) OR (controlled clinical trial) OR (randomized controlled trial[mh]) OR (random allocation[mh]) OR (double-blind[mh]) OR (single-blind[mh])) NOT (animal[mh] NOT human[mh])))))

#7 Search #5 and #6

EMBASE, CCTR, BIOSIS, CLHTA, CINAHL *via* Ovid

1. Clinical trial/
2. Randomized controlled trial/
3. Randomization/
4. Single blind procedure/
5. Double blind procedure/
6. Crossover procedure/
7. Placebo/
8. Randomi?ed controlled trial$.tw.
9. Rct.tw.
10. Random allocation.tw.
11. Randomly allocated.tw.
12. Allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind$.tw.
15. Double blind$.tw.
16. ((treble or triple) adj blind$).tw.
17. Placebo$.tw.
18. Prospective study/
19. or/1–18
20. Case study/
21. Case report.tw.
22. Abstract report/or letter/
23. or/20–22
24. 19 not 23
25. animal/not human/
26. 24 not 25
27. "autologous chondrocyte implantation".mp.
28. "autologous chondrocyte transplantation".mp.
29. exp KNEE/
30. 27 or 28
31. 30 and 29
32. 26 and 31

References

1. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. Arthroscopy 1997;13:456–60.
2. Aroen A, Loken S, Heir S, Alvik E, Ekeland A, Granlund OG, *et al*. Articular cartilage lesions in 993 consecutive knee arthroscopies. Am J Sports Med 2004;32:211–5.
3. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. Arthroscopy 2002;18:730–4.
4. Gerber AC, Hochberg MC, Mead LA. Joint injury in young adults and risk of subsequent knee and hip osteoarthritis. Ann Int Med 2000;133:321–8.
5. Mithoefer K, Williams III RJ, Warren RF, Potter HG, Spock CR, Jones EC, *et al*. The microfracture technique for the treatment of articular cartilage lesions in the knee. A prospective cohort study. J Bone Joint Surg Am 2005;87:1911–20.
6. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. Arthroscopy 2003;19:477–84.
7. Szerb I, Hangody L, Duska Z, Kaposi NP. Mosaicplasty: long-term follow-up. Bull Hosp Jt Dis 2005;63:54–62.
8. Brittberg M. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med 1994;331:889–95.
9. Magnussen RA, Dunn WR, Carey JL, Spindler KP. Treatment of focal articular cartilage defects in the knee: a systematic review. Clin Orthop Relat Res 2008;466:952–62.
10. Jakobsen RB, Engebretsen L, Slauterbeck JR. An analysis of the quality of cartilage repair studies. J Bone Joint Surg Am 2005;87:2232–9.
11. Knutsen G, Drogset JO, Engebretsen L, Grontvedt T, Isaksen V, Ludvigsen TC, *et al*. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. J Bone Joint Surg Am 2007;89: 2105–12.
12. Saris DB, Vanlauwe J, Victor J, Almqvist KF, Verdonk R, Bellemans J, *et al*. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. Am J Sports Med 2009;37(Suppl 1):10S–9S.
13. Nakamura N, Miyama T, Engebretsen L, Yoshikawa H, Shino K. Cell-based therapy in articular cartilage lesions of the knee. Arthroscopy 2009;25:531–52.
14. Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. Int J Epidemiol 2002;31:150–3.
15. SIGN. Scottish Intercollegiate Guideline Network. In. Edinburgh, 2008.
16. Jüni P, Altman D, Egger M. Assessing the quality of randomised controlled trials. In: Egger M, Smith G, Altman D, Eds. Systematic Reviews in Health Care. Meta-Analysis in Context. London: BMJ Publishing Group; 2001:87–108.
17. Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM, *et al*. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg Br 2003;85:223–30.
18. Visna P, Pasa L, Cizmar I, Hart R, Hoch J. Treatment of deep cartilage defects of the knee using autologous chondrograft transplantation and by abrasive techniques – a randomized controlled study. Acta Chir Belg 2004;104:709–14.
19. Dozin B, Malpeli M, Cancedda R, Bruzzi P, Calcagno S, Molfetta L, *et al*. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. Clin J Sport Med 2005; 15:220–6.
20. Horas U, Pelinkovic D, Herr G, Aigner T, Schnettler R. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint: a prospective, comparative trial. J Bone Joint Surg Am 2003;85:185–92.
21. Horas U, Schnettler R, Pelinkovic D, Herr G, Aigner T. [Osteochondral transplantation versus autogenous chondrocyte transplantation. A prospective comparative clinical study]. Chirurg 2000;71:1090–7.
22. Knutsen G, Engebretsen L, Ludvigsen TC, Drogset JO, Grontvedt T, Solheim E, *et al*. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. J Bone Joint Surg Am 2004;86:455–64.

23. Saris DB, Vanlauwe J, Victor J, Haspl M, Bohnsack M, Fortems Y, *et al*. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. Am J Sports Med 2008;36:235–46.
24. Basad E, Stürz H, Steinmeyer J. Die Behandlung chondraler Defekte mit MACI oder Microfracture – erste Ergebnisse einer vergleichenden klinischen Studie. Orthop Prax 2004;40:6–10.
25. Van Assche D, Staes F, Van Caspel D, Vanlauwe J, Bellemans J, Saris DB, *et al*. Autologous chondrocyte implantation versus microfracture for knee cartilage injury: a prospective randomized trial, with 2-year follow-up. Knee Surg Sports Traumatol Arthrosc 2009.
26. Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. J Bone Joint Surg Am 2003;85:58–69.
27. Gudas R, Kalesinskas RJ, Kimtys V, Stankevicius E, Toliusis V, Bernotavicius G, *et al*. A prospective randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint in young athletes. Arthroscopy 2005;21:1066–75.
28. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71–2.
29. Hambly K, Griva K. IKDC or KOOS? Which measures symptoms and disabilities most important to postoperative articular cartilage repair patients? Am J Sports Med 2008;36:1695–704.
30. Tanner SM, Dainty KN, Marx RG, Kirkley A. Knee-specific quality-of-life instruments: which ones measure symptoms and disabilities most important to patients? Am J Sports Med 2007;35:1450–8.
31. Kocher MS, Steadman JR, Briggs KK, Sterett WI, Hawkins RJ. Reliability, validity, and responsiveness of the Lysholm knee scale for various chondral disorders of the knee. J Bone Joint Surg Am 2004;86-A:1139–45.
32. Smith HJ, Richardson JB, Tennant A. Modification and validation of the Lysholm Knee Scale to assess articular cartilage damage. Osteoarthritis Cartilage 2009;17:53–8.
33. Minas T. Autologous chondrocyte implantation for focal chondral defects of the knee. Clin Orthop Relat Res 2001;S349–361.
34. Kreuz PC, Steinwachs MR, Erggelet C, Krause SJ, Konrad G, Uhl M, *et al*. Results after microfracture of full-thickness chondral defects in different compartments in the knee. Osteoarthritis Cartilage 2006;14:1119–25.
35. Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. Am J Sports Med 2009;37:902–8.
36. Henderson I, Lavigne P, Valenzuela H, Oakes B. Autologous chondrocyte implantation: superior biologic properties of hyaline cartilage repairs. Clin Orthop Relat Res 2007;455:253–61.
37. Takahashi T, Tins B, McCall IW, Richardson JB, Takagi K, Ashton K. MR appearance of autologous chondrocyte implantation in the knee: correlation with the knee features and clinical outcome. Skeletal Radiol 2006;35:16–26.
38. Tins BJ, McCall IW, Takahashi T, Cassar-Pullicino V, Roberts S, Ashton B, *et al*. Autologous chondrocyte implantation in knee joint: MR imaging and histologic features at 1-year follow-up. Radiology 2005;234:501–8.
39. Welsch GH, Mamisch TC, Domayer SE, Dorotka R, Kutscha-Lissberg F, Marlovits S, *et al*. Cartilage T2 assessment at 3-T MR imaging: *in vivo* differentiation of normal hyaline cartilage from reparative tissue after two cartilage repair procedures – initial experience. Radiology 2008;247:154–61.
40. Emerson J, Burdick E, Hoaglin D, Mosteller F, Chalmers T. An empirical study of the possible relation of treatment differences to quality scores in controlled randomized clinical trials. Control Clin Trial 1990;11:339–52.
41. Bartlett W, Skinner JA, Gooding CR, Carrington RWJ, Flanagan AM, Briggs TWR, *et al*. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. J Bone Joint Surg Br 2005;87-B:640–5.
42. Gomoll AH, Minas T, Farr J, Cole BJ. Treatment of chondral defects in the patellofemoral joint. J Knee Surg 2006;19:285–95.
43. Minas T, Bryant T. The role of autologous chondrocyte implantation in the patellofemoral joint. Clin Orthop Relat Res 2005;30–9.
44. Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: a systematic review and economic evaluation. Health Technol Assess 2005;9:1–82.
45. Ruano-Ravina A, Jato Diaz M. Autologous chondrocyte implantation: a systematic review. Osteoarthritis Cartilage 2006;14:47–51.
46. Wasiak J, Villanueva E. Autologous cartilage implantation for full-thickness articular cartilage defects of the knee. Cochrane Library 2003.