Comparative analysis of autologous chondrocyte implantation and other treatment modalities: a systematic review

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Abstract

Purpose The purpose of this systematic review was to analyze and determine the effectiveness of autologous chondrocyte implantation (ACI) when compared with other treatment modalities, which includes microfracture, mosaicplasty, abrasionplasty, bone marrow–derived mesenchymal stem cell (BMSC), and matrix-assisted autologous chondrocyte implantation (MACI).

Methods Literature search using online databases PubMed, Scopus, National Institute for Clinical Excellence and Cochrane controlled trial register regarding all cell-based therapies and other interventions for chondral lesions was explored. Data on clinical outcome and repair quality were analyzed. Duplicates and irrelevant articles were omitted.

Result Seventeen (n = 17) studies were included in this review. Among the four trials on ACI versus mosaicplasty, two studies showed no differences in clinical scores, one suggested similar performance while the other suggested better results in tissue quality for ACI. A systematically performed assessment comparing ACI with microfracture shows better clinical outcomes and higher tissue quality after ACI. Studies comparing ACI with MACI or BMSC demonstrated similar results. Although many of these studies had substantial flaws, on the overall, the evidence comparing ACI with other treatment modalities shows better clinical outcomes and higher tissue quality.

Conclusion Despite significant differences between the methodologies employed by different researchers, we can conclude that all except two studies demonstrated ACI being the better treatment for cartilage defects. However, final conclusions regarding long-term effects are still difficult, and therefore, future studies are needed to answer the long-term effects of ACI.

Keywords Autologous chondrocyte implantation · Articular cartilage · Cartilage repair · Review · Systemic

Introduction

Autologous chondrocyte implantation is a surgical approach that has been used to treat defined, symptomatic knee cartilage defects [1]. ACI enables the regeneration of hyaline or hyaline-like cartilage, thereby restoring normal joint function. At present, this procedure is used mainly to treat problems in the knee joints, but its use in many other joints has also been described [2]. Increasing evidence suggests that the only technique so far that enables the regeneration of articular hyaline cartilage in chondral defects is autologous chondrocyte implantation [2]. The use of other biological repair methods for cartilage defects, which includes mosaicplasty and subchondral marrow stimulation, has shown to produce inferior clinical outcomes than ACI although the absolute differences between these groups were quite small to conclude a definite clinical relevance. While the use of ACI has been found to encourage short- to-mid-term results, it lacks further evidence for its long-term effects [3, 4]. Despite the lack of evidence to support the use of ACI against other more cost saving surgical methods, this technique has been deemed in many known literatures to produce true healing rather than
fibrous scarring. Such assumptions, however, need to be backed by more robust evidence. Previous attempts have been made to compare ACI to other treatment modalities through various systemic reviews, but produced inconsistent results with no final conclusions. In addition, these reviews have not analyzed more relevant and recent methods of treating focal cartilage defects that includes matrix-assisted cell therapies and the use of mesenchymal stem cells.

In order to further evaluate the evidence of ACI as the preferred option for knee cartilage repair in a more comprehensive manner, a systematic review of the efficacy using ACI against other treatment modalities was performed. The evidence was measured by determining the clinical efficacy and tissue repair quality using various treatments based on the results of published data. Although there are many papers comparing the two different treatment modalities, there has not been a systemic review which compares all the treatment options to the ACI. In addition, with the availability of more recent published clinical trials describing the long-term effects of ACI, this review may provide further insight into the true efficacy of this treatment modality.

Methods

Search strategy

Online databases including PubMed, Scopus, National Institute for Clinical Excellence (NICE) and Cochrane controlled trial register search were performed. The term “autologous chondrocyte implantation” and “autologous chondrocyte transplantation” was used without restriction to language or date of publication. The results were searched for controlled, randomized, and non-randomized trials and reviewed systematically to obtain the most suitable studies (Fig. 1).

Study selection

All publications of controlled trials up to June 30, 2010, which compared ACI with other treatments for cartilage repair in the knee of humans were selected. Studies were included whether the treatment group received ACI for any cartilage defect in the knee compared with another group receiving other cartilage repair treatments. Case reports, case series, retrospective studies, non-randomized controlled trials, and studies systematically focusing on the combined effects of ACI and other major procedures, such as meniscus replacement, knee ligament repairs, and corrective osteotomies, were excluded from further review.

Data extraction

The data were extracted for the clinical outcomes as well as the clinical evaluation scores. Also, included are the years of follow-up, the demographic of the patient population and also the histological outcomes for each study.

Results

Study characteristics

The online literature search using PubMed, Scopus, National Institute for Clinical Excellence (NICE) and Cochrane Controlled Trial Register found 1,116 scientific papers. After excluding duplicates, 568 were reviewed for suitability. Studies that were included were between the years 2000 and 2010 in English or German and compared different subtypes of ACI with mosaicoplasty (n = 4), microfracture (n = 8), MACI (n = 3), BMSC (n = 1), and abrasionplasty (n = 1) involving a total of 1,644 patients (Table 1).

Clinical outcome

In ACI versus mosaicoplasty, Horus et al. [5, 6] found no significance difference in the clinical scores at 24 months, whereas according to Bently et al. [2] ACI treatment (88%) showed significant improvements to mosaicoplasty (69%). Even though in their study Dozin et al. [7] observed a complete recovery in 68% of ACI-treated patients, they suggest that ACI and mosaicoplasty are clinically equivalent and similar in performance.

In a study conducted by Knutsen et al. [8] which compared ACI with microfracture, no significant difference was observed in the Lysholm scores, however; microfracture produced a better overall functional health and well-being, as observed in the higher SF-36 scores. To determine a longer-term clinical outcome following these procedures, Knutsen et al. [9] followed up the same patient for up to 5 years. They reported no significant differences in the clinical scores or the radiographic results using both methods. Assche et al. [10] had also reported in their series that there were no differences in the clinical outcomes using either method at 2 years of follow-up. However, not all studies appear to support their findings. In a study conducted by Saris et al. [11], the clinical outcome as measured by the knee injury and osteoarthritis outcome score at 12–18 months after characterized chondrocyte implantation was comparable with microfracture. Both treatment groups had a similar mean baseline and both techniques were generally well tolerated. One other study by Saris et al. [12] found that ACI was significantly better in clinical outcomes after 36 months. Similar clinical outcomes were also
observed in a study conducted by Minas et al. [13] and Kon et al. [14].

Of the three studies comparing ACI to MACI, only one study showed MACI was better than ACI [15]. It was also described that ACI showed higher complication rates as compared with MACI. The other two studies reported by Erggelet et al. [3] and Zeifang et al. [16] showed no significant differences in the clinical outcomes. In their studies, MACI was found to be equally effective as ACI in treating focal cartilage defects.

Only one study compares ACI to abrasionplasty. Visna et al. [17] found significantly better results in Lysholm, IKDC, and Tegner scores for patients treated with ACI at 12 months than those who underwent abrasionplasty.

The sole study which directly compares ACI with BMSC demonstrates no significant differences between clinical outcomes. However, Nejadnik et al. [18] concluded in their study that the use of BMSC reduces the treatment cost and is less invasive as compared with ACI. No histological or radiological assessments were performed.

A summary of the clinical and histological outcomes for all the studies included in this review is given in Table 2.

Quality of repair tissue

The quality of repaired tissue was assessed in six of 17 studies reviewed. Most studied described either the ICRS scores or merely used descriptive assessment. In studies comparing ACI and mosaicplasty, according to Horus et al. [5], the postoperative Lysholm score following autologous chondrocyte implantation was inferior to osteochondral transplantation at 6, 12, and 24 months. However, based on the Meyers score and the Tegner activity score, the results were equally good. Histomorphological evaluation of
| Author                | Year | n (ACI/control) | Controls treated with | Reported outcomes                                                                 | Last follow-up at (months) | Average defect size (cm², ACI/control) | Gender ratio (m/f) |
|-----------------------|------|-----------------|-----------------------|-----------------------------------------------------------------------------------|----------------------------|----------------------------------------|------------------|
| Horas et al. [6]      | 2000 | 40 (20/20)      | Mosaicplasty          | (i) Subjective outcome (ii) Lysholm (iii) Tegner                                 | 24                         | 4.4                                    | 23/17            |
| Bentley et al. [2]    | 2003 | 100 (58/42)     | Mosaicplasty          | (i) Cincinnati (i) Stanmore                                                      | 19                         | 4.66                                   | 57/43            |
| Horas et al. [5]      | 2003 | 40 (20/20)      | Mosaicplasty          | (i) Lysholm (ii) Meyers (iii) Tegner (iv) Histology (v) IHC                      | 24                         | 3.86/3.63                              | 23/17            |
| Dozin et al. [7]      | 2005 | 47 (22/25)      | Mosaicplasty          | (i) Lysholm Knee Scoring Scale (i) IKDC                                          | 36                         | 1.97/1.88                              | 27/17            |
| Basad et al. [20]     | 2004 | 19 (10/9)       | Microfracture         | (i) Meyers (II) Lysholm (iii) Tegner (iv) ICRS                                   | 12                         | 3.8/4.2                                | –                |
| Knutsen et al. [8]    | 2004 | 80 (40/40)      | Microfracture         | (i) ICRS (ii) Lysholm (iii) Tegner (iv) SF-36                                   | 2 years                    | 5.1/4.5                                | –                |
| Knutsen et al. [9]    | 2007 | 80 (40/40)      | Microfracture         | (i) ICRS (ii) Lysholm (iii) Tegner (iv) SF-36                                   | 5 years                    | 5.1/4.5                                | –                |
| Saris et al. [11]     | 2008 | 118 (57/61)     | Microfracture         | (i) histology (ii) KOOS (iii) Safety                                             | 18                         | 2.6/2.4                                | 76/42            |
| Saris et al. [12]     | 2009 | 118 (57/61)     | Microfracture         | (i) MRI (ii) KOOS (iii) Safety                                                  | 36                         | 2.6/2.4                                | 76/42            |
| Assche et al. [10]    | 2009 | 67 (34/33)      | Microfracture         | (i) Hop test                                                                     | 2 years                    | 2.5/2.3                                | 46/21            |
| Minas et al. [13]     | 2009 | 321 (211/110)   | Microfracture         | (i) MRI (ii) Failure Rate                                                        | 2 years                    | 4.6/5.2                                | 185/136          |
| Kon et al. [14]       | 2009 | 80 (40/40)      | Microfracture         | (i) IKDC (ii) Tegner (iii) Lysholm                                               | 5 years                    | 2.2/2.5                                | 60/20            |
| Niemeyer et al. [15]  | 2008 | 309 (263/82)    | MACI                  | (i) MRI                                                                         | 4.5 years                  | 4.6                                    | 165/144          |
| Erggelet et al. [27]  | 2009 | 82 (42/40)      | MACI                  | (i) ICRS (ii) Cincinnati (iii) Lysholm                                           | 2 years                    | 6.38/4.6                               | 51/31            |
| Zeifang et al. [16]   | 2010 | 21 (11/10)      | MACI                  | (i) Short Form-36 (ii) Tegner score (iii) Lysholm (iv) Guilquist (v) IKDC         | 2 years                    | 4.1                                    | 16/5             |
| Nejadnik et al. [18]  | 2010 | 72 (36/36)      | BMSC                  | (i) IKDC (ii) ICRS (iii) Short Form-36 (iv) Lysholm (v) Tegner                    | 2 years                    | 3.6/4.6                                | 38/34            |
| Visna et al. [17]     | 2004 | 50 (25/25)      | Abrasion              | (i) Lysholm (ii) IKDC (iii) ICRS (iv) Tegner (v) Histology                       | 12                         | 4.1/3.4                                | 34/16            |
Biopsy specimens within 2 years after autologous chondrocyte implantation demonstrated a complete, mechanically stable resurfacing of the defect in all patients. The tissue consisted mainly of fibrocartilage, while localized areas of hyaline-like regenerative cartilage could be detected close to the subchondral bone. Osteochondral cylinder transplantation or mosaicplasty showed no obvious difference between the transplanted and the surrounding resident cartilage macroscopically. The histological appearance taken at 22 months after osteochondral transplantation showed no degeneration of the articular cartilage. The donor areas were filled with fibrous appearing tissues. However, the results by Bentley et al. [2] contradict the findings of Horas et al. [5]. In their study, Bentley et al. [2] showed that of the 58 patients with lesions treated using ACI, and 51 (88%) had an excellent or good result compared with 29 of 42 (69%) treated by mosaicplasty. Of the 19 biopsies taken from the ACI patients at 1 year, hyaline cartilage of normal appearance was found in seven patients after ACI with normal structure of the cartilage under polarized light and cells in lacunae which were bonded to the calcified zone. The remaining seven patients had both hyaline cartilage

| Table 2 | Clinical and histological outcomes among included studies |
| --- | --- | --- | --- |
| Author | Year | Clinical outcome | Histological outcome | Conclusion |
| ACI vs. mosaicplasty | | | | |
| Horas et al. [6] | 2000 | No difference in clinical scores | Fibrocartilaginous defect filling in ACI, no visible changes in tissue after mosaicplasty | Improvement provided by ACI lagged behind that provided by the mosaicplasty |
| Horas et al. [5] | 2003 | No difference in clinical scores | Fibrocartilaginous defect filling in ACI, no visible changes in tissue after mosaicplasty | Improvement provided by ACI lagged behind that provided by the mosaicplasty |
| Bentley et al. [2] | 2003 | 88% good and excellent after ACI and 69% after Mosaicplasty | 82% good and excellent after ACI, 34% after mosaicplasty | ACI significantly better than mosaicplasty |
| Dozin et al. [7] | 2005 | Complete recovery in 68% after ACI, 88% after Mosaicplasty | No histology | ACI and mosaicplasty are clinically equivalent |
| ACI vs. microfracture | | | | |
| Basad et al. [20] | 2004 | ACI better | No histology | Good clinical result in ACI but only a temporary assessment |
| Knutsen et al. [8] | 2004 | No difference in Lysholm scores but MFX better in SF-36 scores | No difference | Mid-term and long-term follow-up is needed to determine which method is better |
| Knutsen et al. [9] | 2007 | No difference is scores | No histology | No significant difference in the clinical and radiographic results |
| Saris et al. [11] | 2008 | No difference | Better result for ACI | ACI superior to microfracture |
| Saris et al. [12] | 2009 | Improvement after ACI better than MFX | No histology | ACI significantly better clinical outcome after 36 months |
| Assche et al. [10] | 2009 | No significant difference | No histology | ACI similar overall function with microfracture |
| Minas et al. [13] | 2009 | No significant difference | No histology | ACI better results |
| Konet al. [14] | 2009 | ACI better | No histology | Better clinical results for ACI |
| ACI vs. MACI | | | | |
| Niemeyer et al. [15] | 2008 | MACI better | No histology | ACI shows higher complication percentage compared with MACI |
| Erggelet et al. [27] | 2009 | No difference | No histology | MACI equally effective treatment |
| Zeifang et al. [16] | 2009 | No difference | No histology | Superiority of MACI or ACI was not evident |
| ACI vs. BMSC | | | | |
| Nejadnik et al. [18] | 2010 | MSC better | Histology shows hyaline-like cartilage tissue | BMSC reduces cost and less invasive |
| ACI vs. abrasion | | | | |
| Visna et al. [17] | 2004 | ACI better | No histology | Better outcomes in patients treated with ACI |

**Note:** The table above lists clinical and histological outcomes among included studies comparing different treatments for articular cartilage defects.
and fibrocartilage repair, while the other five patients showed fibrocartilage alone. The poor results reported in this study are of mosaicplasty group. In all four studies which compare ACI to mosaicplasty, ACI appears to provide superior healing although not significantly different. Mosaicplasty provided satisfactory outcomes in some patients but in others there was incomplete healing of the space between the grafts and the fibrillation of the repair tissue.

In studies comparing ACI with microfracture, Knutsen et al. [8] reported a lack of significant difference between the ACI and the microfracture groups. Their study showed that 39% of the biopsied specimens had limited amounts of hyaline cartilage, and 43% had fibrocartilage throughout most of their depth. However, there were no significant differences between the frequency with which hyaline and fibrocartilage repair tissues were found. In a study conducted by Saris et al. [11], it was reported that the aspects of structural repair relating to chondrocyte phenotype and tissue structure were superior using chondrocyte implantation than microfracture, while short-term clinical outcome was similar for both treatments. Histological evaluation of the biopsy specimens for BMSC-treated patients by Nejadnik et al. [18] showed hyaline-like cartilage tissue, but there is no histological evidence presented for patients treated with ACI. A summary of the tissue quality outcomes for all the studies included in this review is given in Table 3.

### Table 3 Quality parameters of included studies

| Author          | Year  | Blinding assessors                  | Attrition (%) | % With biopsies | Level of evidence |
|-----------------|-------|-------------------------------------|---------------|-----------------|------------------|
| Horas et al. [6]| 2000  | Histology                           | 5             | 20%             | II               |
| Horas et al. [5]| 2003  | Histology                           | 5             | 20%             | II               |
| Bentley et al. [2]| 2003 | Unclear                             | 0             | 60%             | II               |
| Dozin et al. [7]| 2005  | Surgeon assessed outcomes           | 15.9          | No Bx           | II               |
| Knutsen et al. [20]| 2004 | Histology and clinical              | 0             | 84%             | I                |
| Knutsen et al. [8]| 2007 | Surgeon assessed all                | 0             | No Bx           | I                |
| Basad et al. [9]| 2004  | Primary investigator assessed all   | 0             | No Bx           | I                |
| Saris et al. [11]| 2008 | Histology, clinically self-assessed | 17            | 73%             | I                |
| Saris et al. [12]| 2009 | MRI, clinically self-assessed       | 28            | No Bx           | II               |
| Visna et al. [17]| 2004 | Not specified                       | 0             | 8%              | II               |
| Assche et al. [10]| 2009| Clinically self-assessed            | 0             | No Bx           | –                |
| Minas et al. [13]| 2009| Clinically assessed                 | 0             | No Bx           | IV               |
| Kone et al. [14]| 2009 | Clinically assessed                 | 0             | No Bx           | II               |
| Niemeyer et al. [15]| 2008| Surgeon assessed all                | 0             | No Bx           | IV               |
| Erggelet et al. [27]| 2009| Clinically assessed                 | 10            | 2.4%            | –                |
| Zeifang et al. [16]| 2009| Clinically assessed and MRI         | 0             | No Bx           | II               |
| Nejadnik et al. [18]| 2010| Failure rate                        | 5             | 2.7%            | III              |

### Discussion

Autologous chondrocyte implantation represents a well established and acknowledged therapy for the treatment of isolated cartilage defects of the knee joint. In various comparative studies, ACI produce good clinical outcomes for ≥9 years and the resultant repair tissue resembles hyaline cartilage rather than fibrocartilage [19]. The percentages of satisfactory outcomes in this prospective uncontrolled series were 92% for isolated femoral condyle lesions, 67% for multiple condyle lesions, 89% for osteochondritis dissecans, and 65% for patella. Comparing different cartilage repair publications shows that relatively small, heterogeneous study populations, study center experience, and the effects of different rehabilitation protocols may have confounded results. Owing to a reduced amount of information concerning the therapeutic options, this systemic review evaluates the evidence of options for the cartilage defects and to assess the current evidence for the efficiency of ACI compared with other treatment modalities.

Randomized clinical trials comparing ACI and mosaicplasty were recently published and have been described in few reviews. In the first of these, Horas et al. [5] studied a group of 40 patients with large articular lesions of the femoral condyle and showed somewhat better results in the group of patients treated with mosaicplasty. On the contrary, Bentley et al. [2] reported ACI being significantly superior to mosaicplasty, as mosaicplasty appears to deteriorate...
After 1 year. The study also gave some evidence that ACI is valuable for selected patients, and it also dramatically reduces the symptoms of pain and disability. The continued use of mosaicplasty, however, appears to be dubious [2]. Thus, these prospective but independent and separate studies provide conflicting results in terms of relative efficacy of ACI and mosaicplasty. At the same time, they indicate that the two procedures appear to meet the needs of the orthopedic community to treat focal cartilage lesions efficiently and reliably.

Likewise, similarly good short-term clinical results were also obtained when comparing ACI to microfracture. ACI and microfracture yielded similar results at 2−5 years follow-up as described by Knutsen et al. [9]. Even though there appears to be a significant improvement in both groups; there was a 23% rate of treatment failure in each group. The authors also reported that larger lesions, in particular those bigger than 4 cm², performed worse with microfracture, whereas no such size correlation was seen in the ACI group. They concluded that bigger lesions might be better treated with ACI. Peterson et al. [19] reported a failure rate of 11% after autologous chondrocyte implantation on the femoral condyles, with most of the failures occurring less than 2 years postoperatively. Their clinical success rate has been quoted to be from 80 to 90%, and they concluded that a graft surviving for 2 years is likely to remain viable 3−8 years later. Another study comparing ACI and microfracture [13] states that there was an increased failure rate of ACI after previous treatment with marrow stimulation techniques. Basad et al. [20] reported significant differences between autologous chondrocyte implantation and microfracture in terms of both absolute values and the degree of improvement of Lysholm scores. These differences are clinically relevant as the patient would be able to perceive the differences entailed with this outcome measure. However, Saris et al. [11] concluded that ACI resulted in a significantly better structural cartilage regeneration and better clinical outcome at 12 months when compared with microfracture.

There has been only one published study that compares ACI to stem cell therapy. In an observational cohort study conducted by Nejadnik et al. [18], BMSC and ACI provided similar improvement in clinical outcomes. They have a comparable improvement in quality of life, health, and sport activity with men reporting greater improvements than women. This study, however, did not assess the tissue quality repair. Wakitani S et al. [21] demonstrated a better arthroscopic and histological result in BMSCs for femoral condyle cartilage defects repair compared with the control group (no cell).

Despite the theoretical and proven advantage of an increased proportion of hyaline cartilage after autologous chondrocyte implantation as demonstrated by its improved histological scores, the lack of long-term data in the other reviews precluded a statement of superiority of one cartilage repair or restoration technique over another. The findings of this systematic review have confirmed those of several recent systematic reviews [22−24]. Even though many of those recent reviews had small differences regarding study inclusion and exclusion criteria, study methodological assessment tools, and surgical techniques analyzed, their conclusions were quite similar. This systemic review’s unique strength includes the inclusion and discussion of high-level evidence with inclusion and exclusion criteria developed to properly achieve the aims of the study, comparing autologous chondrocyte implantation with BMSC and MACI techniques, comparison of different generations of autologous chondrocyte implantation, the identification of factors that influence outcomes after autologous chondrocyte implantation, and the identification of factors that predict better outcomes with autologous chondrocyte implantation as compared with non-autologous chondrocyte implantation techniques. The recent addition of high-quality randomized trials not included in previous reviews supplements the existing literature and may show a trend toward better outcomes after autologous chondrocyte implantation [11, 22, 25].

Another limitation of existing studies relates to the follow-up time. No long-term results related to ACI are available. But in those performed by the other investigators, patients were monitored for no longer than 2−3 years. In all but two studies [2, 3], the shortest follow-up time was not below 2 years. However, in several studies of ACI, unsatisfactory results for patients and surgeons were observed. The incidence of such unsatisfactory results varies from 10 to 30%, depending on studies and location of the transplant [3, 9, 26].

Conclusion

ACI is associated with superior structural regeneration of cartilage tissue and thus better clinical outcome can be deducted from the existing literature when compared with other treatment modalities. Among the included studies, there is much inconsistency in the methodological quality and findings. Regardless of these problems, the absolute differences between treatment groups are fairly small, thus raising questions about their clinical importance beyond mere statistical significance. However, final conclusion is still difficult, and therefore, future studies are needed to answer the long-term effects of ACI.

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