



## Use of chondral fragments for one stage cartilage repair: A systematic review

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### Abstract

**AIM:** To investigate the state of the art regarding Cartilage Autograft Implantation System (CAIS) or Particulated Juvenile Allograft Cartilage (PJAC).

**METHODS:** The authors searched the English literature regarding CAIS and PJAC. The search strategy was: (particulated cartilage) OR autologous cartilage fragments. All basic science articles were included. Clinical articles with less than 10 patients treated and less than 6 mo of follow-up were excluded. With these criteria, a total of 17 articles were available for the present review.

**RESULTS:** PJAC and CAIS are relatively novel techniques for cartilage repair. Good basic science evidence was described to support the concept. Although the preliminary clinical reports show encouraging results, clinical data are still limited, especially for CAIS. The indications for both techniques need to be precisely defined (age of the patients, size of the lesion, and involvement of the subchondral bone), together with other debated issues.

**CONCLUSION:** In conclusion, the authors can state that encouraging preliminary results are available for both techniques. However, further studies are necessary to precisely determine the indications, surgical techniques, and long term outcomes for PJAC and CAIS.

**Key words:** Cartilage; Juvenile; Chondral fragments; Adult; Particulated cartilage

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**Core tip:** In this systematic review regarding Cartilage Autograft Implantation System (CAIS) and Particulated Juvenile Allograft Cartilage (PJAC), basic science and clinical articles with more than 10 patients treated and more than 6 mo of follow-up were included. A total of 17 articles were available for the present review. Good basic science evidence *in vitro* and *in vivo* was described to support the concept of CAIS. Only one level II paper reported the clinical results of the CAIS technique. On the other hand, little basic science evidence and 4

preliminary clinical trials are available regarding the PJAC technique. CAIS and PJAC represent promising single step solutions for cartilage restoration with hyaline-like repair. However, many controversies still exist regarding both techniques, including the indications (age of the patients, size of the lesion, and involvement of the subchondral bone).

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## INTRODUCTION

Chondral and osteochondral lesions are common in orthopedics, and their treatment still remains a challenge for the orthopedic surgeon. The overall prevalence of full-thickness focal chondral defects of the knee in athletes has been estimated around 36% (2.4%-75% between all studies)<sup>[1]</sup>. Depending on the characteristics of the patient and the lesion (symptoms, previous surgeries, involvement of subchondral bone, size, and chronicity of the defect), different options are available for the treatment of focal chondral defects, and these include: Bone marrow stimulation techniques (*i.e.*, microfractures), osteochondral auto/allograft transplantation, and autologous chondrocyte implantation (ACI). All of these techniques have advantages and disadvantages. Although ACI showed to result in hyaline-like repair and better outcomes than simple microfractures<sup>[2,3]</sup>, two surgeries and an expensive laboratory cell expansion are necessary. In order to solve these drawbacks, new single-step solutions were described. Recently, the use of cartilage fragments has been introduced, as a single step chondral repair technique. These can be freshly harvested autologous cartilage chips held in the defect by a scaffold [Cartilage Autograft Implantation System (CAIS)] or Particulated Juvenile Allograft Cartilage (PJAC). The goal of this study is to present the state of the art regarding these two techniques, including basic science and clinical results.

## MATERIALS AND METHODS

The authors performed a search in the literature to identify basic science and clinical articles (Level I to IV) that would include the CAIS and PJAC techniques.

The authors searched the PubMed database for English literature regarding this topic in May 2015. The search strategy was as follows: (particulated cartilage) OR autologous cartilage fragments. The search produced 62 articles and 39 articles were excluded by title, leaving 23 papers for the present review. Clinical articles with less than 10 patients treated and less than 6 mo of follow-up were excluded. With these criteria, 10 articles

were excluded by abstract, leaving 13 articles for the present review. No articles were excluded after reading the full text version. In addition, relevant references not identified by the database search, but cited by the downloaded articles and matching the inclusion criteria, were included. In this way 4 more papers were included, for a total of 17 articles for the present review<sup>[4-20]</sup>.

## RESULTS

### CAIS

**Basic science (*in vitro*):** Six *in vitro* basic science studies reported the results of CAIS technique<sup>[4-9]</sup>.

In 2011, Bonasia *et al.*<sup>[4]</sup> co-cultured adult and juvenile cells (part 1) as well as adult and juvenile cartilage fragments (part 2).

Cartilage donors were 3 adult and 3 juvenile patients. In part 1, juvenile and adult chondrocytes were co-cultured with 5 different proportions: 100%, 50%, 25%, 12.5%, and 0%. The cells were cultured three-dimensionally with low-melt agarose. Isolated juvenile cultures showed better biochemical and histologic scores than mixed and adult cultures. No significant differences were described between co-cultures (1:1) and adult cultures. In part 2, chondral fragments were used (< 1 mm): adult, juvenile, and adult-juvenile co-cultures (1:1). Mixed cartilage fragment showed better proteoglycans/DNA ratio ( $P = 0.014$ ), percentage of safranin O-positive cells ( $P = 0.012$ ), Bern score ( $P = 0.001$ ), and collagen type II than adult cultures. No significant differences were noted between juvenile and mixed groups<sup>[4]</sup>.

In 2012, Marmotti *et al.*<sup>[5]</sup> evaluated cultures of rabbit cartilage fragments on Petri dishes, a paste scaffold with injectable hyaluronic acid (HA), and a membrane scaffold with an HA-derivative felt. At 60 d, a time-dependent cell outgrowth from cartilage fragments was observed with both types of scaffolds. Chondrocyte migration was less with Petri dishes than with scaffolds. At 2 mo, neo-matrix was evident and the migrated chondrocytes showed a roundish shape. Newly formed tissue was positive for collagen type II immunostaining. A marked reduction in volume was observed in the paste scaffold at 1 and 2 mo, with approximately a 50% of shrinkage from the initial volume after 2 mo<sup>[5]</sup>.

In another study published in 2013, Marmotti *et al.*<sup>[6]</sup> compared *in vitro* the cell outgrowth from human cartilage fragments of adult and young donors using two different types of scaffolds (HA-derivative injectable paste scaffold and HA-derivative membrane scaffold) and evaluated the influence of transforming-growth-factor- $\beta$ 1 (TGF- $\beta$ 1) and granulocyte colony-stimulating factor (G-CSF) on chondrocyte behavior. The histological analysis showed age-dependent and time-dependent chondrocyte migration. A significant difference ( $P < 0.05$ ) was observed between young and older donors. No difference was detected between the two types of scaffolds. After 1 mo, the number of migrating

cells/area significantly increased due to exposure to TGF- $\beta$ 1 and/or G-CSF ( $P < 0.05$ ). Immunofluorescence revealed that outgrowing cells from unstimulated scaffold sections were positive for SOX9, CD151, CD49c and G-CSF receptor. Immunofluorescence of cells from construct cultures showed an increase in  $\beta$ -catenin in all stimulated groups and an increased Proliferating Cell Nuclear Antigen expression in G-CSF-exposed cultures ( $P < 0.05$ )<sup>[6]</sup>.

In 2013, Marmotti *et al.*<sup>[7]</sup> studied the use of cartilage fragments seeded on a HA scaffold + platelet-rich fibrin matrix (PRFM) and fibrin glue (FG). Chondrocyte migration on the scaffolds was evident at 15, 30, and 60 d. At 30 d, high cellularity and intense extracellular matrix (ECM) production were described. At 60 d, ECM was positive for collagen type II<sup>[7]</sup>.

In 2014, Wang *et al.*<sup>[8]</sup> tested the effect of knee-joint-specific bioreactor-induced dynamic compression and shear on minced bovine cartilage fragments cultures. The authors noticed that this method of culture was feasible under *in vitro* free-swelling and dynamic loading conditions, simulating *in vivo* post-transplantation. Mechanical stimulation significantly provoked cellular outgrowth and long-term chondrogenic maturation at the mRNA level, whereas histology depicted immature neotissue (weaker collagen type II and aggrecan expression with an increased collagen type I expression) where typical cartilage matrix was expected<sup>[8]</sup>.

In 2015, Bonasia *et al.*<sup>[9]</sup> evaluated *in vitro* if the degree of chondral fragmentation affected ECM production, in cartilage fragment autograft implantation. The cartilage was taken from five donors undergoing total hip replacement and minced in order to obtain 4 groups with different fragment sizes: (1) "fish scale" (diameter 8 mm, thickness 0.3 mm); (2) cubes with 2 mm side; (3) cubes with 1 mm side; and (4) cartilage paste (< 0.3 mm). The authors observed that ECM production was significantly affected by the degree of chondral fragmentation. At biochemical evaluation (Proteoglycans/DNA ratio), group 4 performed significantly better than group 1 ( $P < 0.001$ ) and 3 ( $P = 0.02$ ), while group 2 performed better than group 1 ( $P = 0.03$ ). At histological evaluation (Bern score), group 4 performed significantly better than group 1 ( $P = 0.02$ ), 2 ( $P = 0.04$ ), and 3 ( $P = 0.03$ ). One of the limitations of this study were the use of arthritic cartilage<sup>[9]</sup>.

**Basic science (*in vivo*):** Six basic science studies reported the *in vivo* results of CAIS technique<sup>[5,7,10-13]</sup>.

The use of autologous cartilage fragments for the repair of chondral defects was first described by Albrecht *et al.*<sup>[10]</sup> in a rabbit model. The authors compared two groups: defects left untreated (23) and treated with autologous cartilage fragments and FG (52). Untreated defects showed no hyaline-like repair tissue. On the other hand, chondrocyte proliferation, hyaline-like repair, and alcian blue-positive ECM were evident in the cartilage fragment group<sup>[10]</sup>.

In 2006 Lu *et al.*<sup>[11]</sup> studied the CAIS technique in a

goat model. Eight skeletally mature goats were used. Two full thickness 7-mm-diameter chondral defects on each side of the trochlear ridge were created through a mini-arthrotomy. The defects were either left untreated (empty) or treated with scaffolds loaded with cartilage fragments or with the scaffold alone. The scaffolds were fixed with a single PDS/PGA staple (DePuy Mitek, Norwood, MA). The technique produced hyaline-like repair tissue at 6 mo<sup>[11]</sup>.

In 2008, Lind *et al.*<sup>[12]</sup> investigated the cartilage repair of autologous cartilage chips or ACI with a collagen membrane in a goat model. Sixteen full-thickness cartilage defects (diameter 6 mm) were created in the femoral condyles of 8 adult goats. At 4 mo, no difference was found in O'Driscoll and Pineda histology scores, tissue filling (35%), or repair tissue stiffness between the two groups<sup>[12]</sup>.

In a similar study, Frisbie *et al.*<sup>[13]</sup> compared empty defects, CAIS technique and ACI in a horse model (10 skeletally mature horses). Arthroscopic, histologic, and immunohistochemistry results showed superiority of both implantation techniques (ACI and CAIS) compared with control groups, with CAIS achieving the highest score<sup>[13]</sup>.

In 2012, Marmotti *et al.*<sup>[5]</sup> compared the repair tissue of 5 different groups of treatment in a rabbit model (50 adult rabbits): cartilage fragments loaded onto HA scaffolds with FG (group 1) or without FG (group 2); scaffolds alone with FG (group 3) or without FG (group 4); empty defects (group 5). At 6 mo, cartilage fragment-loaded scaffolds induced significantly better repair tissue (in terms of histological modified ICRS score and a modified O'Driscoll scale) than the scaffold alone groups. Repair in group 2 was superior compared with the control groups ( $P < 0.05$ )<sup>[5]</sup>.

In 2013, Marmotti *et al.*<sup>[7]</sup> studied in a goat model a culture-free approach to osteochondral repair with minced autologous cartilage fragments loaded onto a scaffold composed of a HA-derived membrane, PRFM and FG. Two unilateral osteochondral defects were created in 15 adult goats. The defects were assigned to 3 different treatments: (1) cartilage fragments + HA scaffold + PRFM + FG; (2) HA scaffold + PRFM + FG; and (3) left untreated. Hyaline-like repair tissue was evident in group 1, in terms of morphological, mechanical and histological assessments<sup>[7]</sup>.

**Surgical technique:** According to the original technique for CAIS described by Cole *et al.*<sup>[14]</sup>, hyaline cartilage is arthroscopically harvested (through standard anteromedial and anterolateral portals) from a low load-bearing surface (*e.g.*, lateral wall of the intercondylar notch or trochlear ridge with an amount similar to ACI, roughly 200 mg), using a specifically designed device that minces the cartilage into 1- to 2-mm pieces. After harvest, the device (DePuy Mitek, Raynham, Massachusetts) uniformly disperses the minced cartilage onto the biodegradable scaffold. The scaffold consists of an absorbable copolymer foam of 35% polycaprolactone

and 65% PGA, reinforced with a PDO mesh (Advanced Technologies and Regenerative Medicine). The fragments are secured to the scaffold using FG. The joint is approached through a small arthrotomy, the defect is debrided to the level of the subchondral bone, and vertical walls of normal cartilage are created. A template of the defect is then obtained, using a sterile paper. The scaffold is trimmed according to the template and implanted on the defect with the chondral fragments in contact with the subchondral bone. Fixation can be achieved with bioabsorbable staples<sup>[14]</sup>.

**Clinical results:** Only one paper (level II) reported the clinical results of the CAIS technique<sup>[14]</sup>. Cole *et al.*<sup>[14]</sup>, in a randomized controlled trial, compared autologous cartilage fragment repair (CAIS technique) with microfractures, in 29 patients with 2-years of follow-up.

General outcome measures (*e.g.*, physical component score of the SF-36) indicated an overall improvement in both groups, and no differences in the number of adverse events were noted between the groups. At 24 mo, the authors described significantly higher International Knee Documentation Committee (IKDC) score and Knee injury and Osteoarthritis Outcome Score (KOOS) for the CAIS group, compared to the microfracture group. No differences were noted between the groups in terms of MRI qualitative analysis. However, the microfracture group showed a higher risk of developing intralesional osteophytes. The authors concluded that the new technique is a safe, feasible, and effective method for the treatment of focal chondral defects<sup>[14]</sup>.

## PJAC

**Basic science (*in vitro*):** Only one paper described the *in vitro* behaviour of juvenile cartilage fragments cultures<sup>[4]</sup>. In 2011, Bonasia *et al.*<sup>[4]</sup> compared *in vitro* cultures of isolated adult, isolated juvenile and mixed juvenile/adult chondrocytes (part 1) and chondral fragments (part 2). The results of this study were previously described in the basic science (*in vitro*) section for the CAIS technique<sup>[4]</sup>.

**Basic science (*in vivo*):** Only one paper described the results *in vivo* (small animal model) of the PJAC technique<sup>[4]</sup>. In 2015, Bonasia *et al.*<sup>[4]</sup> evaluated the repair of chondral lesions treated with combined autologous adult/allogenic juvenile cartilage fragments, compared with isolated adult and isolated juvenile cartilage fragments in a rabbit model. Fifty-eight adult and 5 juvenile rabbits (cartilage donors) were used. A large osteochondral defect was created in the center of the femoral trochlea of adult rabbits. Four treatment groups were created: Group 1 = untreated defects (controls); Group 2 = adult cartilage fragments; Group 3 = juvenile cartilage fragments; and Group 4 = adult + juvenile cartilage fragments. The defects were evaluated with ICRS macroscopic score, modified O'Driscoll score, and Collagen type II immunostaining. At 6 mo, group

4 showed higher modified O'Driscoll score ( $P = 0.003$ ) and Collagen type II immunostaining score ( $P < 0.001$ ) than group 1. Histologically, also group 3 performed better than group 1 ( $P = 0.03$ ), and group 4 performed better than group 2 ( $P = 0.004$ )<sup>[15]</sup>.

**Surgical technique:** After arthroscopic evaluation through standard anteromedial and anterolateral portals, a limited medial or lateral arthrotomy is performed to fully visualize the lesion.

The defect is outlined with a scalpel to create vertical peripheral walls and the damaged cartilage debrided to the subchondral bone. A sterile foil is used to create a three-dimensional template of the defect. One package of DeNovo NT graft (DeNovo NT® Natural Tissue Graft, Zimmer Inc, Warsaw, Indiana, United States) can cover defects of about 2.5 cm<sup>2</sup>. The preservation medium is removed and the chondral fragments positioned in the template 1 to 2 mm apart. The template is then filled with FG to within 1 mm of its full depth. Once the FG is solid, the fragment/glue construct is separated from the foil. The construct is fixed to the bed of the defect with FG. Alternatively, the particulated cartilage can be directly applied into the defect and glued *in situ*<sup>[16]</sup>.

**Clinical results:** Four papers describing the clinical results of PJAC and matching the inclusion criteria were found<sup>[17-20]</sup>.

In 2013, Coetzee *et al.*<sup>[17]</sup> described the clinical outcomes of patients treated with PJAC for symptomatic osteochondral lesions in the ankle. Twenty-four ankles were included (average age of the patients at surgery 35 years, average lesion size 125 mm<sup>2</sup>, mean follow-up 16.2 mo). At final follow-up, the average American Orthopaedic Foot and Ankle Society Ankle-Hindfoot Scale was 85, with 18 (78%) ankles reporting good to excellent scores. Good results were also obtained in terms of Short-Form 12 Health Survey (SF12) physical composite score, SF12 mental health composite score, Foot and Ankle Ability Measure activities of daily living and Sports, as well as visual analog scale for pain<sup>[17]</sup>.

In 2013, Tompkins *et al.*<sup>[18]</sup> evaluated the outcomes and MRI findings after PJAC for the treatment of focal Outerbridge grade 4 articular cartilage defects of the patella. Fifteen knees (13 patients) were enrolled, with a mean age at surgery of 26.4 years, and a mean follow-up of 28.8 mo. The mean International Cartilage Repair Society cartilage repair assessment score on MRI was 8.0 ± 2.8, a nearly normal assessment. Of 15 knees, 11 (73%) were found to have normal or nearly normal cartilage repair. The mean fill of the defect was 89% ± 19.6%, with 12 of 15 knees (80%) showing at least 90% defect coverage. The mean IKDC score was 73.3. The median score for the Kujala survey was 79. The median score on the Tegner activity scale was 5 (range, 3 to 9), and the mean score on the visual analog scale for pain was 1.9<sup>[18]</sup>.

In 2014, Farr *et al.*<sup>[19]</sup> described the results of PJAC in



patients with symptomatic articular cartilage lesions on the femoral condyles or trochlear groove of the knee, in a 2-year follow-up prospective study.

Twenty-five patients with a mean age of 37 years were included. At 2 years, some patients underwent voluntary knee arthroscopy and cartilage biopsy. Histological analysis included safranin O staining for proteoglycans and immunostaining for type I and II collagen. At 2 years, the IKDC and KOOS (for pain, symptoms, activities, and sports) scores significantly improved. The MRI evaluation reported results similar to normal hyaline cartilage. Eight patients underwent arthroscopic biopsy and the repair tissue was considered a mixture of hyaline and fibrocartilage, positive for type II collagen, and integrated with the surrounding cartilage<sup>[19]</sup>.

In 2014, Buckwalter *et al.*<sup>[20]</sup> retrospectively evaluated 13 cases of chondral lesion of the patella, treated with PJAC. The mean age was 22.5 years and the mean follow-up was 8.2 mo. Tibial tubercle anteromedialization was performed in 6 patients. The overall KOOS score significantly improved from a mean of 58.4 to 69.2 ( $P = 0.04$ )<sup>[20]</sup>.

## DISCUSSION

PJAC and CAIS are relatively novel techniques for cartilage repair. Good basic science evidence was described to support the concept. Although the preliminary clinical reports show encouraging results, clinical data are still limited, especially for CAIS. The indications for both techniques need to be precisely defined (age of the patients, size of the lesion, and involvement of the subchondral bone), together with other debated issues.

The controversies regarding these techniques include: (1) No data are available regarding the optimal degree of cartilage fragmentation, related to increased matrix production. Some recent research suggested that fragmentation to pieces smaller than 1 mm (basically to a cartilage paste) is related to increased ECM production. However this *in vitro* study was conducted on arthritic cartilage and these data need to be confirmed on juvenile fragments and non arthritic patients<sup>[9]</sup>; (2) No data are available regarding the use of CAIS and PJAC associated with scaffolds. If the theory that fragmentation to smaller pieces results in increased matrix production is confirmed, the use of scaffolds might become necessary to keep the cartilage paste in place; and (3) Some basic science studies suggested that mixing allogeneic juvenile and autologous adult cartilage fragments, increased ECM production. These data need to be confirmed in large animal models and in clinical trials<sup>[4,15]</sup>.

In conclusion, the authors can state that encouraging preliminary results are available for both techniques. However, further studies are necessary to precisely determine the indications, surgical techniques, and long term outcomes for PJAC and CAIS.

## COMMENTS

### Background

Chondral and osteochondral lesions are common in orthopedics, and their treatment still remains a challenge for the orthopedic surgeon. Different options are available for the treatment of focal chondral defects: bone marrow stimulation techniques, osteochondral auto/allograft transplantation, and autologous chondrocyte implantation. All of these techniques have disadvantages (*i.e.*, non-hyaline like repair or two-staged procedures).

### Research frontiers

To overcome these limitations, tissue engineering is prospecting new single-step solutions, including the use of cartilage fragments. These can be freshly harvested autologous cartilage chips held in the defect by a scaffold [Cartilage Autograft Implantation System (CAIS)] or Particulated Juvenile Allograft Cartilage (PJAC). The goal of this study is to present the state of the art regarding these two techniques, including basic science and clinical results.

### Innovations and breakthroughs

This is the first systematic review regarding CAIS and PJAC. A total of 17 articles were available for the present review. Good basic science evidence *in vitro* and *in vivo* was described to support the concept of CAIS. Only one level II paper reported the clinical results of the CAIS technique. On the other hand, little basic science evidence and 4 preliminary clinical trials are available regarding the PJAC.

### Applications

CAIS and PJAC represent promising single step solutions for cartilage repair. However, many controversies still exist regarding both techniques, including the indications (age of the patients, size of the lesion, and involvement of the subchondral bone).

### Terminology

CAIS: Cartilage Autograft Implantation System; PJAC: Particulated Juvenile Allograft Cartilage.

### Peer-review

The manuscript is interesting.

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