Introduction

Autologous chondrocyte implantation (ACI) is a two-stage surgical technique employed to address full thickness, symptomatic chondral lesions. Initially, it involves a cartilage biopsy, isolation and expansion of chondrocytes \textit{ex-vivo}, and subsequent re-implantation into the damaged joint. Chondrocyte seeded porcine collagen membrane as graft composite is considered to be the next generation ACI techniques, and the cell seeded graft can be fixed to the subchondral bone without suture. Encouraging clinical outcomes using a chondrocyte seeded collagen membrane (matrix-induced ACI - MACI) have been reported in the knee\textsuperscript{4,10,14,24,32,43} and ankle.\textsuperscript{8,15,17,27,34} With the development of surgical techniques both knee and ankle ACI permit arthroscopic delivery of the scaffold,\textsuperscript{9,12,13,15,16,20,24-26,29,35,40} which may permit accelerated rehabilitation and minimize the morbidity of arthrotomy including reducing the risk of complications such as adhesions, joint stiffness, excessive pain and scarring.

While a range of surgical options exist for addressing cartilage defects in the shoulder including debridement, microfracture, osteochondral autograft transfer (OATS) and osteochondral allografts,\textsuperscript{11,18,41} published evidence reporting on ACI in the glenohumeral joint is limited to one case report (humeral head)\textsuperscript{39} and one small case series (n=4),\textsuperscript{5} of which three cases were also on the humeral head. We describe the surgical technique and clinical and radiological outcomes to 24 months in a young patient undergoing arthroscopic ACI for a symptomatic cartilage defect on the glenoid.

Keywords: autologous chondrocyte implantation; arthroscopic; clinical outcomes; magnetic resonance imaging; shoulder; glenohumeral joint.
Case Report

A 25-year-old female nurse presented with pain and functional limitation of her dominant right shoulder, following a direct blow to the anterior aspect of her shoulder from another player during a game of Gaelic football. This resulted in severe pain immediately, though there was no reported sensation of an obvious glenohumeral dislocation or subluxation. Due to persistent discomfort and a painful arc high resolution magnetic resonance imaging (MRI) was undertaken 6 days post-injury, demonstrated a large shear injury to the glenoid articular surface from 9 o’clock to 6 o’clock, with a chondral defect measuring 14mm (antero-posterior) by 10mm (cranio-caudal). The displaced chondral fragment was visualised in the anterior joint, and the labrum and glenohumeral ligaments were unremarkable, as were other supporting bony and soft tissue structures. The patient was otherwise well, a non-smoker with no other medical history, nor any prior shoulder symptoms or injuries.

First Stage Arthroscopy and Cartilage Harvest

An arthroscopy was performed 14 days post-injury to evaluate the extent of the injury and remove the displaced cartilage fragment, as well as harvest donor cells for ACI. A standard shoulder arthroscopy was performed in the lateral position with a posterior and anterior portal. The loose fragment was found in the anterior inferior joint space (Figure 1A) and was removed and seen to be purely cartilaginous (Figure 1B). This was sent to the laboratory (Orthocell, Perth, Western Australia), where chondrocytes were isolated from the tissue and cultured for approximately 4-8 weeks. At this time, the joint was further evaluated, and the rotator cuff, long head of biceps and humeral articular surface were all normal. The full thickness articular cartilage defect was identified on the glenoid (Figure 2A), while the posterior glenoid chondrolabral junction was torn and mobile, but not grossly unstable. Two
Y knot 1.3 mm anchors (Conmed Linvatec, Largo FL) were used to stabilize the posterior labrum (Figure 2B). Simple sutures were passed with a Spectrum MVP passer (Conmed Linvatec, Largo FL). This provided a defect with well-defined and stable margins for the second stage graft implantation. Post-operatively the patient was managed in a simple sling for comfort. Range of motion was limited to avoid internal rotation and lifting with this arm was limited to 2 kg to avoid loading and damaging the margins of the defect.

Autologous Chondrocyte Implantation

The second stage re-implantation was performed 8 weeks later. A standard lateral arthroscopy was performed. Posterior and anterior (just above subscapularis in the rotator interval) portals were created and two 8 x 75 mm DryDoc cannulas (Conmed Linvatec, Largo FL) were inserted. There are no internal valves in these cannulas and the outer caps were removed to allow easy passage of the graft during the dry arthroscopy. A viewing portal was placed high in the rotator interval just below long head of biceps (Figure 3A). The joint was assessed, and fibrous material had partially filled the defect (Figure 3B), which was debrided to subchondral bone with curette (Figure 3C).

Fluid was then drained from the shoulder, and a long metal sucker was used to maintain a dry working environment, ensuring the defect bed was dry. An adrenaline soaked patty was used on the subchondral bone to further dry the area and provide haemostasis. Two vials (approximately 4.91 million cells per 1ml vial) totalling approximately 9.82 million cells (chondrocytes) were extracted into a 2 ml syringe using a 19 gauge needle, and then dropped intra-operatively onto the porous side of a Type I collagen membrane (size of 3x4 cm²). The chondrocytes were at passage 3 when seeded onto the membrane. This collagen membrane was supplied for cell seeding according to the Therapeutic Goods Administration (TGA)
approved manufacture procedure for Ortho-ACI (Australian Register of Therapeutic Goods listed product code is 289402, https://www.tga.gov.au/artg/artg-id-289402). After a 20 minute incubation period in a small container at room temperature, chondrocytes were integrated into the three-dimensional porous collagen membrane. A surgical pen was employed to mark the membrane to aid in subsequent arthroscopic implantation, and the membrane was then trimmed based on the template made by the foil (from a suture pack) to ensure a good fit without any overhang. Once the membrane shape and size was confirmed, two 2-0 vicryl sutures with a taper needle were passed under the labrum at the edge of the defect with a Spectrum MVP passer (Conmed Linvatec, Largo FL). The suture ends were left long through the anterior and posterior cannulas, with care taken not to cross the sutures. The anterior suture ends with the needles were passed through the graft in the corresponding edge at a similar position. The needles were cut off and a simple knot made to prevent the suture pulling through the seeded chondrocyte membrane.

The seeded chondrocyte membrane graft was then folded in half and passed through the anterior cannula with an arthoscopic grasper, and the vicryl sutures were shortened from the posterior cannula as the graft was introduced. Once in the joint, the graft was unfolded and left loose away from the defect. Fibrin sealant (Tisseel®, Baxter International, Illinois, U.S.) was placed in the defect using a long spinal needle through the anterior cannula (Figure 3D). The graft was then placed, using the arthroscopic grasper to guide and pulling on the vicryl sutures to dock the graft, and a silicone foley catheter was then passed through the cannulas from posterior to anterior (Figure 3E). The tip was held with the arthroscopic grasper to control the position of the balloon, and the catheter inflated with normal saline. This was employed to provide an even pressure to the membrane and allowed visualisation of the graft through the balloon. Pressure was maintained for a 30 second period, to ensure the fibrin glue
becomes adherent and provided uniform graft stability. The shoulder was then taken through a range of motion to ensure graft stability. The vicryl suture ends were then cut flush (Figure 3F), and the portals were closed. The shoulder was placed in a simple sling.

Post-operative Management

The patient underwent a coordinated post-operative rehabilitation program of progressive exercise and graduated loading over 6 months, while further education and advice was provided up until the 12 month time-point. Initially, the patient was immobilized in a sling for six weeks post-operatively during daily activities (removed for rehabilitation exercises). Following passive range of motion (ROM) exercises over the first 1-2 weeks, the out-patient program was initiated at 2-weeks post-surgery and included early scapula positioning and active-assisted (progressing toward active) ROM exercises, strengthening exercises initially employing therabands, cables and pulleys from 3-4 weeks, and progressive open and closed kinetic chain strengthening as tolerated from six weeks onwards.

Clinical Outcome Measures

Clinical assessment was undertaken pre-surgery and at 3, 6, 12 and 24 months post-surgery, using: 1) the Oxford Shoulder Score (OSS); 2) the Upper Extremity Functional Scale (UEFS); 3) the Disability of the Arm, Shoulder and Hand (DASH) questionnaire; 4) a Visual Analogue Pain Scale assessing the frequency (VAS-F) and severity (VAS-S) of pain; 5) a Global Rating of Change (GRC) scale; 6) a Patient Satisfaction Questionnaire, and; 7) the Constant Score. The OSS is a 12-item questionnaire evaluating pain and function, and an improvement of 6 points has been reported as the minimal detectable change (MDC). The UEFS is a 20-item survey reporting on upper limb function, and an MDC of 9.4 has been reported. The DASH is a 30-item questionnaire evaluating pain, symptoms and physical
function, as well as work and sport capacity, in patients with upper limb musculoskeletal disorders. An MDC for the DASH has been reported as 12.7 points. The VAS required the patient to rate their pain frequency (0 = never, 10 = constant) and intensity (0 = no pain, 10 = worst pain imaginable) on a 0-10 cm sliding scale in the preceding 24 hours. A 1.4cm improvement on the VAS has previously been reported as the minimal clinically important change (MCID) in patients undergoing non-operative treatment for rotator cuff disease.

The Constant Shoulder Score has been validated for total shoulder arthroplasty, rotator cuff repair, adhesive capsulitis of the shoulder, and proximal humeral fractures. The subjective component of the Constant score is allotted a total of 35 points and evaluates patient-reported pain (15 points), as well as how the patient’s shoulder condition affects their ability to undertake occupational, leisure and other daily activities (20 points). Active ROM is allotted 40 points consisting of forward flexion (10 points), abduction (10 points), functional external rotation (10 points) and internal rotation (10 points). Maximal pain-free isometric shoulder abduction strength in 90° of shoulder abduction in the scapular plane is allotted 25 points. Finally, a ‘total’ Constant score was calculated (0-100) by summing the three individual subscales. The MDC for the Constant score has been reported as 18 points for rotator cuff tears.

An 11-point Global Rating of Change (GRC) scale was employed to evaluate the patient’s perceived current status compared to before their surgery, ranging from -5 (very much worse) to 0 (about the same) to 5 (completely recovered). Finally, a patient satisfaction questionnaire was employed to evaluate the patient’s level of satisfaction with their surgery overall, as well as their satisfaction with surgery to relieve their shoulder pain, improve their ability to perform normal daily and work activities, improve their ability to return to recreational activities (e.g. swimming, golf) and improve their ability to participate in sporting activities.
e.g. tennis, squash). A categorical tool was employed: 1 = very satisfied; 2 = somewhat satisfied; 3 = somewhat dissatisfied; 4 = very dissatisfied.

Radiological Evaluation

High resolution MRI was undertaken pre-surgery and at 4, 12 and 24 months post-surgery, using 1.5T and 3T clinical scanners (Ingenia, Philips Healthcare, Best, Netherlands). Standardized proton density and T2-weighted fat-saturated images were obtained in coronal-oblique and sagittal-oblique planes (slice thickness 3-3.5mm, field of view 14cm, minimum 512 matrix in at least one axis). Additional axial proton density fat-saturated images were obtained (slice thickness 3.5mm, field of view 14cm, minimum 480 matrix in at least one axis).

We sought to evaluate eight pertinent parameters of graft repair (graft infill, signal intensity, border integration, surface contour, tissue structure, effusion, subchondral lamina and bone), following the magnetic resonance observation of cartilage repair tissue (MOCART) scoring system. The eight defined parameters were each scored from 1-4 (1=poor; 2=fair; 3=good; 4=excellent) in comparison to the adjacent native cartilage. An MRI composite score was then calculated (scored 0-4) by multiplying each individual score by a weighting factor, and adding the scores together. MRI evaluation was performed by an independent, experienced musculo-skeletal radiologist.
Results

Clinical Outcome
A significant clinical improvement was seen in all scores over time, with the maximum possible score attained for each patient-reported outcome measure by 24 months post-surgery and all MDCs were exceeded over this time (Table 1). The patient perceived their shoulder to be fully recovered by 24 months as per the GRC, and the patient was ‘very satisfied’ with the surgery for relieving pain, improving their ability to perform normal daily and work activities, and improving their ability to return to recreational activities. The patient was ‘satisfied’ with the surgery for improving their ability to participate in sporting activities.

Radiographic Outcome
MRI demonstrated a progressive infill in regenerative tissue and signal intensity up until 12 months, sustained to 24 months. At 24 months, the graft was isointense and full, comparative to the adjacent native cartilage, with a smooth surface and imperceptible border zone integration (Figure 4). As per the MOCART scoring system, graft infill was scored as 0 (poor = subchondral bone exposed), 3 (good = >50% height of adjacent cartilage), 4 (complete = level with the adjacent native cartilage) and 4, at pre-surgery and 4, 12 and 24 months post-surgery, respectively. The overall MOCART MRI composite score was graded as 1.35, 2.80, 3.95 and 4.00 (out of 4.00) at the aforementioned time points.
Discussion

This single case study presents a successful outcome following third-generation ACI performed on the glenoid, with improved clinical and radiological outcomes to 24 months post-surgery. While outcomes are encouraging following ACI in other joints such as the knee and ankle, published evidence of its use in the glenohumeral joint is limited to one case report (humeral head) and one small (n=4) case series, of which three cases were also on the humeral head.

The single case by Romeo et al. employed first generation periosteal-covered ACI, though no specific clinical outcomes were reported apart from the manuscript stating that ROM was full at 12 months post-surgery with no further patient complaints of pain at rest or with weather changes. Furthermore, first-generation techniques are more surgically complex, may result in extensive micro-trauma and cell leakage, have donor morbidity from periosteal harvest, increased rates of graft hypertrophy and require more exposure for suturing the cover, therefore not permitting arthroscopic surgical techniques. Buchman et al. further reported on four cases undergoing ACI (autologous chondrocyte transplantation collagen membrane seeding - ACT-C) in the glenohumeral joint (3 humeral head, 1 glenoid), with encouraging clinical outcomes reported at a mean follow up of 41.3 ± 24.9 months (range 11-71 months).

In determining the best surgical option for cartilage defects in the glenohumeral joint, a number of factors must be considered including defect location, size, depth and containment, as well as concurrent pathology that must be addressed at the time of surgery. Alternative surgical procedures for this patient may have included microfracture (with or without augmentation) or OATS. In a randomized controlled trial, Saris et al. demonstrated that by
215 24 months post-surgery the use of matrix-applied characterized autologous cultured chondrocytes was clinically and statistically significantly better than microfracture, albeit this was in the differently behaving knee joint and in symptomatic cartilage defects ≥3cm². While lower compressive loads may occur across the glenohumeral joint (compared with the knee and ankle), high shear stress may occur given the large ROM and speed of rotation that occurs in this joint, and ACI was deemed the most appropriate option when considering her age and requirement for a more sustainable tissue repair. Furthermore, given the relative scarcity of published evidence on glenohumeral ACI and associated rehabilitation protocols, the protocol followed was developed based on clinical experience in treating other shoulder pathologies, combined with knowledge gained from treating patients embarking on ACI in the knee and ankle.
Conclusion

The management of focal cartilage defects in the glenohumeral joint remains a challenge. This case study presents a successful outcome following arthroscopic third-generation ACI performed on the glenoid, combined with a structured rehabilitation protocol. Improved clinical outcomes and a high level of patient satisfaction was observed to 24 months post-surgery, with evidence of regenerative tissue repair sustained to 24 months, similar in characteristics to the adjacent native glenoid articular cartilage. Larger case series are required to better evaluate whether ACI can provide a good therapeutic option for patients presenting with symptomatic cartilage defects in the glenohumeral joint.
ACI in the glenohumeral joint

References


ACI in the glenohumeral joint


ACI in the glenohumeral joint


ACI in the glenohumeral joint


Tashjian RZ, Deloach J, Porucznik CA, Powell AP. Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease. J Shoulder Elbow Surg 2009;18:927-932. 10.1016/j.jse.2009.03.021


Table Legends

Table I. Overview of pre- and post-operative clinical outcomes.
**Figure Legends**

409  **Figure 1.** Identification of the loose fragment in the anterior inferior joint space at the time of first stage arthroscopic surgery (A), which was seen to be purely cartilaginous (B).

410

411  **Figure 2.** Identification of the full thickness glenoid defect (A), with subsequent stabilization of the posterior labrum (B).

412

413  **Figure 3.** Sequence demonstrating the second-stage surgical implantation procedure, including (A) the viewing portal placed high in the rotator interval just below the long head of biceps, (B) identification of the partially filled defect with fibrous material at the time of second-stage implantation, (C) with subsequent debridement of tissue, (D) introduction of the fibrin sealant via a long spinal needle through the anterior cannula, (E) placement of the graft and introduction of the silicone foley catheter which was instilled with saline, and (F) final appearance of the graft.

414

415  **Figure 4.** Coronal T2-weighted fat saturated images, demonstrating: (A) pre-operative image of the full-thickness glenoid chondral defect, (B) at 4 months following surgery the chondral graft is hyperintense to native cartilage and chondral fill is between 50-100% of the native cartilage thickness, and (C) at 12 months and (D) 24 months following surgery the chondral graft is isointense and approximates the thickness of native cartilage.