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**Does Autologous Chondrocyte Implantation Provide Better
Outcomes Than Microfracture in the Repair of Articular Knee
Defects?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For the Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

OBJECTIVE: The objectives of this selective EBM review is to determine whether or not Autologous Chondrocyte Implantation is more effective than microfracture in the repair of articular knee defects.

STUDY DESIGN: Review of three English language primary studies published in 2009 and 2010.

DATA SOURCES: Randomized controlled trials comparing Autologous Chondrocyte Implantation and Microfracture found using PubMed, MedLine and Cochrane Database.

OUTCOMES MEASURED: Clinical outcome measured by the Knee Injury and Osteoarthritis Outcome Score (KOOS). The primary measure of outcome was evaluated using the KOOS questionnaire with subdomains of ADL's, pain, symptoms, stiffness and quality of life. KOOS data was compared between treatment groups for patients with symptom onset less than 2 years vs more than 2 years and less or more than 3 years. Serial MRI scans were scored using Magnetic resonance Observation of Cartilage Repair Tissue (MOCART) system. A rehabilitation protocol was implemented where components were evaluated pre surgery and at 6, 9, 12 and 24 months post surgery. Patients are followed up 8-12, 22-26, 50-54 weeks post operatively for efficacy and safety evaluations.

RESULTS: Three randomized controlled trials were included in this review. The study by Basad indicated ACI as having significantly more effective outcomes over 2 years compared to microfracture. Saris' study provided similar conclusions, offering improved outcomes with ACI after 36 months. However, Van Assche's study had similar overall functional outcomes for both ACI and MF.

CONCLUSIONS: Based on findings upon analysis of three RCT's, Autologous chondrocyte implantation provides significant improvement in articular knee defects allowing improved function, mobility and activity as compared to that of microfracture.

KEY WORDS: Autologous chondrocyte implantation, microfracture

Introduction:

ACI is an advanced cell based technique for treatment of cartilage defects. Damage to the articular cartilage limits activity level as well as the ability for reparation and restoration of the knee. Intact articular cartilage is needed for normal joint movement and decreased friction through range of motion. The first stage of autologous chondrocyte implantation begins with arthroscopic sampling of cartilage from an area of limited weight bearing, typically from the medial or lateral femoral condyle¹. Chondrocytes are then isolated where they can then be grown in vitro for 4 to 6 weeks². An area of the periosteum is then harvested and formed into a periosteal patch that will be sutured over the area of damaged cartilage³. A tight seal will be formed so that once the cells are reimplanted they will be held in place at the site of injury³. The cells are then reimplanted into the damaged area of articular cartilage through arthrotomy. The autologous cells will adapt by forming new cartilage into the area of the defect³.

ACI is an appropriate treatment for small tears of the cartilage. It is not to be used for widespread wear of the cartilage such as with arthritis¹. The patient must have a stable knee without associated ligament damage, must be of healthy BMI and have failed with nonoperative treatments¹. Femoral condyle injuries are very common in athletes and ACI can be an effective technique for repair in the field of orthopedic surgery. This is especially useful for patients opting out of total knee replacements. The total cost for the ACI procedure falls between \$17,600 and \$38,400⁶. A patient of ACI would have multiple healthcare visits yearly due to the preoperative imaging needing to visualize the level of damage, the 2 steps in the procedure, where 6 weeks after the cells are taken the patient will have them reimplanted, as well as the post op follow up imaging and physical

exam along with necessary physical therapy. Follow up visits vary depending on level of pain, range of motion and disability levels. Articular cartilage defects are often due to sports related trauma. Due to its avascular nature it has poor ability to repair itself. Focal articular cartilage defects are often the source of pain and functional issues and so early diagnosis is important in appropriate management¹⁰. Articular defects if untreated can lead to additional injuries including menisci and cruciate ligament injuries¹⁰.

First line treatment typically includes debridement and lavage by which loose articular tissue debris is removed¹⁰. However, such management may solely have short term effects. Microfracture is another technique that is frequently used. Subchondral bone is disrupted in an attempt to initiate stem cell migration to the site of the defect¹⁰. Conservative treatments should always primarily be used. These include NSAID use, steroid injections, physical therapy¹¹. Patients with severe injury may undergo total knee replacements where prosthetic tibial, femoral and posterior patellar surfaces are implanted¹¹.

ACI is an appropriate treatment for small tears of the cartilage. It is not to be used for widespread wear of the cartilage such as with arthritis. It is a promising new treatment for full thickness articular cartilage defects. ACI restores the cartilage whereas microfracture simply covers up the defect.

Objective: The objective of this selective EBM review is to determine whether or not ACI is more effective than microfracture in the repair of articular cartilage knee injuries.

Methods: The chosen studies were all randomized controlled trials. The populations included were patients with symptomatic cartilage defects of the knee. The interevention of Autologous Chondrocyte Implantation was compared to Microfracture. Measured

outcomes include level of function, range of motion, mobility, strength, stiffness and activity of daily life. A detailed search was completed through use of search engines Pubmed, MedLine, and Cochrane database. Keywords “Autologous chondrocyte implantation” and “Microfracture” were used in combination to search for English-language articles. All of the resulting qualified articles were published between 2009 and 2010 in peer reviewed journals. The patients included people between the ages of 18 and 50 with articular knee injuries. Excluded however were people with the presence of inflammatory arthritis, instability of the knee joint, prior or planned meniscectomy of over 30% of the meniscus, BMI >30, varus or valgus deformity, osteonecrosis, osteoarthritis or chondrocalcinosis. For this review, selected dichotomous data were interpreted by using statistics including P-values, NNT, RRR and ARRR.

Table 1 - Demographics & Characteristics of included studies

Study	Type	# of Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Intervention
Basad, Ebran, 2010	RCT	60	18-50	-Symptomatic cartilage defects -Post traumatic -Single isolated chondral defects of the femoral condyle or patella.	The presence of chronic inflammatory arthritis, instability of the knee joint, prior or planned meniscectomy of over 30 % of the meniscus, BMI greater than 30, varus or valgus deformity, osteonecrosis, osteoarthritis or chondrocalcinosis.	3	Microfracture
Saris, Daniel, 2009	RCT	118	18-50	Single International Cartilage Repair Society grade III/IV symptomatic cartilage defects of the femoral condyles in a stable, well	No exclusion criteria noted	33	Microfracture

				aligned knee with minimal additional injury, agreeing to comply with a strict rehabilitation protocol			
Van Assche, 2009	RCT	67	18-50	-Local cartilage defects w mean size 2.4 cm of the femoral condyle of the knee -Symptomatic single cartilage lesions of the femoral condyle between 1 and 5 cm -Agreed to actively participate in strict rehabilitation and follow up programs.	No exclusion criteria noted	13	Microfracture

Outcomes Measured:

Clinical outcome measured by the Knee Injury and Osteoarthritis Outcome Score (KOOS). The primary measure of outcome was evaluated using the KOOS questionnaire, a validated self reported assessment consisting of 5 separately scored subdomains: ADL's, pain, symptoms, stiffness and quality of life. KOOS data was compared between treatment groups for patients with symptom onset less than 2 years v. more than 2 years and less or more than 3 years. Serial MRI scans were scored using Magnetic resonance Observation of Cartilage Repair Tissue (MOCART) system. MRI scans were taken 1 week post operatively to check for delamination and graft hypertrophy. A rehabilitation protocol was implemented for both active knee flexion and extension range, anterior laxity, knee extension strength and single leg hop performance. All were evaluated pre surgery and at 6, 9, 12 and 24 months post surgery. Patients are followed up 8-12, 22-26,

50-54 weeks post operatively for efficacy and safety evaluations. Tegner scores are taken for activity level, Lysholm scores for pain, stability, gait and clinical symptoms. ICRS scores were also used.

Results:

Three Randomized Controlled Trials were used to compare the outcomes of chondral knee defects upon the use of ACI versus MF.

Van Assche's study used a significant level set at $P < 0.05$ and confidence interval of 95 %. Active knee flexion improved for both groups, but extension and anterior laxity remained unchanged. Single hop performance was improved more so with MF than ACI. At 6 months both groups had decreased functional performance, but because it was less pronounced in those with MF, these patients recovered to pre-surgery levels of performance at 9 months. However, both groups had small yet significant outcomes between 12 and 24 months. Most importantly, functional recovery at 2 years is comparable for both groups. Patients with recent osteochondritis dissecans, advanced osteoarthritis, ligament instability and malalignment greater than 5 degrees were excluded. The Number Needed to Treat was calculated to be 4.76, therefore for every 5 patients, 1 more patient had improved outcomes compared to the control (Table 2). However, the Number Needed to Harm was 16.67, so for every 17 patients 1 person worsened compared to the control group (Table 3)

In Basad's study there were no significant differences except symptom duration which was .3 years longer in the Microfracture group. The difference between baseline and 2 years post operatively for Lysholm scores for both groups were significant with a $P < .0001$. However, the ACI group was more effective over time with a $P = 0.005$. The

Lysholm score rates a patients pain, swelling, mobility, limp, locking sensation, squatting ability, stair climbing ability, and giving out sensation on a scale. Tegner scores were also monitored which measures the patients activity level. This is measured preoperatively and postoperatively. ACI ($P < 0.0001$) was also significantly more effective over time than MF ($P=0.04$). Patients with osteochondral defects were withdrawn and 3 patients dropped out; One without reason, one became pregnant and the other was an early treatment failure. Significance level was set a 5 %. The Number Needed to Treat was 100 therefore, for every 100 people treated with ACI, 1 more patient had improved outcomes compared to the control group (Table 2).

Saris’ study did not provide enough information to convert to dichotomous data because the outcomes measured were unable to be categorized into two mutually exclusive groups. The median duration of symptoms was longer for patients receiving ACI than MF. ACI patients symptoms lasted nearly 2 years whereas MF patients lasted about a year and a half. Mean improvements of ADL’s, pain, symptoms, stiffness, quality of life and sports were all greater in the ACI group. At 36 months, more patients responded to ACI for KOOS responder analysis. KOOS represents the Knee Injury and Osteoarthritis Outcome Score.

Table 2. Efficacy of ACI in Treatment of Chondral Defects: NNT

Study	Control Event Rate (CER)	Experimental Event Rate (EER)	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Number Needed to Treat (NNT)
Basad, 2010	.09%	.1%	.111%	.01%	100
Saris, 2009	N/A	N/A	N/A	N/A	N/A
Van Assche, 2009	.62%	.83%	.339%	.21%	4.76

Table 3. Efficacy of ACI in Treatment of Chondral Defects: NNH

Study	Control Event Rate	Experimental Event Rate	Relative Risk Increase	Absolute Risk Increase	Number Needed to Harm
Van Assche, 2009	.82%	.88%	.073%	.06%	16.67

Saris' study provides plentiful data on safety assessment. 67% of people receiving ACI treatment and 59% of MF patients experienced at least one adverse effect over the entire 36 months of recovery. However, these numbers decreased to 32% and 33% respectively from 18 months to 36 months. Majority of adverse effects were mild to moderate yet 25% of both ACI and MF patients experienced at least one severe adverse effect. More patients receiving Microfracture experienced a significant adverse effect than did those with ACI. Arthralgia was the most common adverse event for both groups. However, patients with ACI had more joint swelling, crepitus and cartilage hypertrophy. 3 patients of the Microfracture group withdrew due to their undesirable outcomes, whereas no patients of ACI were discontinued for such reasons.

Basad's study provided no treatment related safety issues and any irritation experienced was eased through the use of NSAIDs. One patient in the ACI group had persistent pain after one year.

The study created by Van Assche mentions a limitation in which the patients as well as the physical therapists were not blinded to the treatment allocation. Future studies could overcome this by at least blinding the assessor to the knee of injury. One could do so simply by keeping the knees covered during treatment.

Discussion:

Controversy still exists as to whether Microfracture or Autologous Chondrocyte Implantation is the best repair technique. Injuries they should be used for are also still

being investigated. Many attempts to repair damaged articular cartilage have been met with issues such as inability to produce hyaline cartilage, poor integration with the surrounding cartilage, and gradual deterioration of the repair tissue⁸. ACI was first used in 1987 and has been performed on more than 12,000 patients internationally⁸. Carticel is currently the only FDA approved technique for culturing of chondrocytes⁴. In 1997, Carticel received FDA approval for the repair of clinically significant, symptomatic cartilaginous defects of the femoral condyle caused by acute or repetitive trauma⁴.

ACI has demonstrated significant benefits for patients in terms of diminished pain and improved function. This treatment however continues to be very strictly regulated. It is currently the most widely researched clinical cartilage repair technique. Despite the fact that ACI has been in clinical use for more than 15 years, the evidence for the outcomes is lacking. Although this may be the procedure of the future, it does still have downsides including the potential leakage of chondrocytes from defects, the uneven distribution of cells, and the risk of periosteal complications⁸. Early problems include periosteal graft detachment and delamination as well as late periosteal hypertrophy⁸. When repairing articular defects it is important to initially diagnose and correct any significant comorbidities such as meniscus injury, ligament laxity, or malalignment of the tibiofemoral or patellofemoral joint⁸. Uncorrected meniscal deficiency and ligament laxity are a contraindication to cartilage restoration procedures. The ACI procedure is predominantly for lesions larger than 2 cm⁸. Over 100 payers have medical policies that cover Carticel, including Cigna, Prudential, and United Healthcare. Over 50% of the 43 independent Blue Cross and Blue Shield Association members representing 25 States allow coverage for ACI⁹.

Conclusion:

Although there is conflicting evidence in the current literature, 2 of the 3 RCT's indicate improved outcomes with ACI as compared to MF. Both Saris and Basad's studies demonstrated significantly better treatment in symptomatic articular defects. Therefore, I agree with such studies in that ACI provides improved function, mobility and activities of daily life moreso than with treatment with Microfracture. va

Autologous chondrocyte implantation is used to repair defects in the articular cartilage. When the cartilage is injured the chondrocytes lose their ability to regenerate causing loss of function and often immobility. With ACI, chondrocytes are taken from nonweight bearing portion of the femur, sent to a lab and cultured for reimplantation. 6 weeks later new chondrocytes are implanted into the patient at the site of the articular cartilage injury¹. The 2 primary goals for an ACI rehabilitation program are adaptation and remodeling of the repair as well as return to function⁸. The 3 main components of the rehabilitation program are progressive weightbearing, restoration of range of motion, and enhancement of muscle control and strengthening⁸. The repair site is at its most vulnerable during the first 3 months after ACI⁸. At this time, it is important to avoid impact as well as excessive loading and shearing forces. It is difficult to assess the effectiveness of ACI and its long-term results however many studies are underway in search of answers. Research is lacking in terms of force such grafts can endure. Future studies should focus on the stresses necessary to disrupt or delaminate the graft. ACI could be the treatment of the future as it will reduce the surgical morbidity associated with open arthrotomy⁸.

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