Knee Articular Cartilage Restoration: From cells to the patient

Professor Lars Engebretsen, University of Oslo, Norway
Much of this started in 1994:

- I 1989 Grande et al - cartilage cell transplantation into rabbit femur
- Brittberg et al, New England Journal of Medicine i 1994 - clinical study
Treatment of Deep Cartilage Defects in the Knee with Autologous Chondrocyte Transplantation
Mats Brittberg, Anders Lindahl, Anders Nilsson, Claes Ohlsson, Olle Isaksson, and Lars Peterson

Volume 331:889-895 October 6, 1994 Number 14
The problem we are trying to solve:

- Cartilage lesions grade III/IV >2 cm²
- Trauma or OCD
- Posttraumatic OA
Injury to articular cartilage of the knee

- Meniscus injury (13 %)
- OCD (100 %)
- ACL injuries (6.4 %)
- PCL injuries (9.9 %)
- Chondral fractures (100 %)
Effect of Gender and Sports on the Risk of Full-Thickness Articular Cartilage Lesions in Anterior Cruciate Ligament–Injured Knees
A Nationwide Cohort Study From Sweden and Norway of 15 783 Patients

1. Jan Harald Røtterud, MD†‡, Einar A. Sivertsen, MD, PhD†, Magnus Forssblad, MD, PhD§‖, Lars Engebretsen, MD, PhD¶# and Asbjørn Årøen, MD, PhD¶#

2. †Department of Orthopedic Surgery, Akershus University Hospital, Lørenskog, Norway
   ‡Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, Norway
   §Capio Artro Clinic AB, Stockholm, Sweden
   ‖Stockholm Sports Trauma Research Center, Karolinska Institutet, Stockholm, Sweden
   ¶Oslo Sports Trauma Research Center, Oslo, Norway
Do they all have pain?
KOOS 05/06 all patients (n=84) and reference population 35-54 yrs*

So today: What’s best and are we getting better?
Treatment of the cartilage pathology
J. Richard Steadman, MD

• The “father” of Microfracture
• Began in early 1980’s with an ice pick!
Microfracture: still a good choice?

Yes:

- Well proven over time
  - Steadman papers
- Easy surgery
  - But difficult rehab
- Inexpensive and less surgery
  - However, not good if later ACI or MACI?
Microfracture: still a good choice?

No:

- Increase in failures with time
  - Trend, but no firm data
- Decreased return to sports in athletes
  - No RCTs
- Decreased results in ACI after microfracture
  - One study
- Increased sclerosis in subchondral bone
  - Animal studies
Clinical application of ACI


- Biopsy of healthy cartilage
- Defect
- Periosteal flap sutured over lesion
- Injection
- Periosteum
- >10 x in number
- Suspension of chondrocytes
- Monolayer culture for 11-21 days
- Enzymatic digestion

Suspension of chondrocytes >10 x in number
Autologous Chondrocyte Implantation Compared to Microfracture in the Knee: A Randomized Trial

By Gunnar Knutsen, MD, Jon Olav Drogset, MD, PhD, Lars Engebretsen, MD, PhD, Tom C Jon Olav Drogset, MD, Torbjørn Grøntvedt, MD, PhD, Eirik Solheim, MD, Sally Roberts, PhD, Vidar Isaksen, MD, and Oddmund Johansen, MD

Investigation performed at University Hospital Tromsø, Tromsø, Oslo Orthopaedic University Clinic, Deaconess University Hospital Bergen, Bergen, Norway, and Robert Jones and Agnes Hunt Orthopaedic Hospital, Shrewsbury, United Kingdom

Background: New methods have been used, with promising results, to treat full-thickness articular cartilage lesions. The present study was to compare autologous chondrocyte implantation (ACI) trial with microfracture (MF) treatment. We are not aware of any previous randomized studies comparing these methods.

Methods: Thirty patients with cartilage defects were included in the study. Forty patients were treated with autologous chondrocyte implantation, and forty were treated with microfracture. The cartilage repair systems were used in all patients. The patients were randomized to either ACI or MF treatment. The clinical outcome was assessed using the Knee Society score and the International Cartilage Repair Society (ICRS) score.

Results: The results of the present study showed that both methods were equally effective in improving the clinical outcome. The ICRS score improved significantly in both groups, with no statistically significant differences between the two groups. The Knee Society score also improved significantly in both groups, with no statistically significant differences between the two groups.

Conclusions: Both methods provided satisfactory results in 77% of the patients at five years. The results of the present study provide evidence for the use of either method in the treatment of full-thickness cartilage lesions.

Level of Evidence: Level 1a. See instructions to Authors for a complete description of levels of evidence.
Age and activity

- Younger patients (less than 30 yrs. old) in both groups have significant better results.
- More active patients (Tegner) in both groups have also significantly better clinical scores (Lysholm, VAS and SF 36)
Potential disadvantages of ACI (1)

The risk of leakage of transplanted chondrocytes
Potential disadvantages of ACI (2)

An uneven distribution of chondrocytes in the transplanted site due to gravity *(Sohn, 2002)*
Potential disadvantages of ACI (3)

The reacquisition of phenotypes of dedifferentiated chondrocytes in a monolayer culture

Can dedifferentiated chondrocytes re-express the articular chondrocyte phenotype after transplantation?

Monolayer culture for 4 weeks

(Benya & Shaffer Cell 1982)
Hyaline cartilage = Cells + Matrix
Figure 1: The process toward filling the defect. Design: A syringe is used to inject adjacent cartilage in order to avoid any irritation of the adjacent cartilage.

Oslo Sports Trauma Research Center

the bottom of the bone directed toward the bottom of the bone plate

and suturing around the

age repair was convened that article describes and including more detailed
Matrix-induced ACI (MACI)

- from Cell transplantation to Tissue transplantation

Autologous chondrocytes + Scaffold

MACI (Cherubino 2003)
AUTOLOGOUS CHONDROCYTE TRANSPLANTATION ON 3D SCAFFOLD

CHONDRAL

- Collagen matrices type I, type II
- fibrin
- hyaluronan
- hydrogel

OSTEOCHONDRAL

- cellular fibrin glue and a calcium-phosphate
- poly (D,L) lactide-co-glycolide + B-tricalciumphosohate

ANIMAL STUDY

PILOT CLINICAL STUDY

IN CLINICAL PRACTICE

- HA (Hyalograft)
- Collagen
  - MACI
  - CaRes
  - CoDoN
  - NeoCart
- PGA/PLA fleece
- Alginate

Oslo Sports Trauma

RESEARCH CENTER
Cartipatch®: in order to make implantation easier and to promote redifferentiation, a tri-dimensional algarose-alginate matrix was developed. It is evaluated in an ongoing phase II clinical trial.
MaioRegen®
HOW IT WORKS (1/2)

- Preparation of the implant site
- Shape MaioRegen®
- MaioRegen® implant

- MaioRegen® house into the defect
- Restoring of anatomical continuity
- In situ self-stabilization
HOW IT WORKS (2/2)

- MSC migration
- Cell-adhesion
- Cell-colonization of the overall structure

- Synthesis of either bone or cartilage matrix
- Resorption and remodeling
- Tissue regeneration
Advantages of MACI over ACI

- The technical and theoretical advantages
  a. Less invasive technique including the arthroscopic technique because of no need to harvest periosteum
  b. Decreased surgical time, morbidity, and complications or graft failures caused by a periosteal flap
- Homogeneous distribution of chondrocytes and the maintenance of the phenotype
- Better clinical outcomes
Clinical application of scaffolds for cartilage tissue engineering

Junji Iwasa · Lars Engebretsen · Yosuke Shima · Mitsuo Ochi

Randomized clinical trials and longer follow-up periods are needed for more widespread information regarding the clinical effectiveness of MACI!
Are Mesenchymal Stem Cells better than chondrocytes in cartilage repair?
MSC

- Minor morbidity
- Large numbers available
- One stage procedure possible
- Older patients can be treated?
- Biological potential for cartilage repair increased
- Clinically undocumented

Chondrocytes

- Morbidity of concern
- Able to make cartilage
- Result in fibrocartilage
- Improved symptom score
- Most suited for patients under age of 50?
- Return to work with knee load difficult
- 10-25 % reoperations
HA+MSC vs empty HA in rabbits

- The defects were filled with HYAFF®-11 + MSC in one knee and empty HYAFF®-11 in the other
- $10 \times 10^6$ cells/cm$^2$
Bone marrow mesenchymal stem cells in a hyaluronan scaffold for treatment of an osteochondral defect in a rabbit model

S. Laken · B. Jakobsen · A. Åsen · S. Heir · A. Shahdadfar · J. E. Brinchmann · L. EngerRetsen · F. P. Reinholt

Received: 30 October 2007 / Accepted: 6 May 2008 / Published online: 1 July 2008
© Springer-Verlag 2008

Abstract The purpose of this study was to evaluate the efficiency of using mesenchymal stem cells (MSC) in a hyaluronan scaffold for repair of an osteochondral defect in rabbit knee. Bone marrow was harvested from the posterior iliac crest in 11 New Zealand White rabbits. MSC were isolated and cultured in autologous serum for 28 days and transferred to a hyaluronan scaffold 24 h prior to implantation. A 4 mm diameter and 1.5 mm deep defect was created in the medial femoral condyle of both knees and the scaffold with MSC was implanted in one knee while an empty scaffold was implanted in the contralateral knee. After 24 weeks the rabbits were killed and histological sections were subjected to semiquantitative and quantitative evaluation by observers blinded regarding treatment modality. High degree of filling was obtained, but there was no statistically significant difference between the two treatments. However, there was a tendency for a better quality of repair in the MSC treated knees. No hyper trophy was observed by either method. MSC in a hyaluronan scaffold may be a promising treatment approach, but further studies are needed to determine the best combination of scaffold and cells.

Keywords Mesenchymal stem cells · Autologous transplantation · Articular cartilage · Hyaluronic acid · Tissue engineering · Surgery · Knee · Rabbits

Introduction

Focal cartilage and osteochondral injuries are common [1] and injured articular cartilage has limited capacity for complete spontaneous healing. With the aim of increasing the healing potential, autologous chondrocyte implantation (ACI) was introduced, and the first clinical results using this approach in treatment of human knees were published in 1994 [5]. In this so-called first generation chondrocyte implantation procedure, the defect is covered by a periosseous flap sutured to the rim of the defect and the chondrocytes as a cell suspension are implanted under the flap. The second generation chondrocyte implantation procedure involves the use of autologous chondrocytes implanted in scaffolds [4, 29]. With both first and second generation approaches the chondrocytes are harvested from the joint and then expanded in vitro. In this process the cells dedifferentiate and lose their ability to produce
Randomized clinical trials and longer follow-up periods are needed regarding the clinical effectiveness of stem cells.
MSC-ACI

- Theoretical, larger potential to regenerate articular cartilage
- One surgery
- Chondrocyte harvesting is reported to reduce knee function
- Current results 75% in 75% of the patients
Transplantation

Scaffolds
ChondroGide
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>MSC</th>
<th>ACI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean (Range)</td>
<td>34 (18-44)</td>
<td>29 (19-45)</td>
</tr>
<tr>
<td>Gender M:F</td>
<td>6:5</td>
<td>6:6</td>
</tr>
<tr>
<td>Area Mean cm²</td>
<td>3.6 (1.8-7)</td>
<td>3.0 (1.2-5.8)</td>
</tr>
<tr>
<td>Medial Femoral Condyle</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Lateral Femoral Condyle</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Mean number of cells implanted</td>
<td>$58.6 \times 10^6$</td>
<td>$34.5 \times 10^6$</td>
</tr>
<tr>
<td>OCD/Chondral</td>
<td>2/11</td>
<td>5/13</td>
</tr>
</tbody>
</table>
Current re

- MSC
  - N = 11
  - F = 3

- ACI
  - N = 13
  - F = 0
  - E = 1
Surgical repair versus non-operative management

- No studies
- Ongoing RCT at Oslo University Hospital:
  - Comparison of two different surgical repair technique
  - Includes evaluation of improvements in knee function following a 3 months pre-operative rehabilitation program
Inclusion

- Referred patients to UUS (N = 320)
- Candidates for cartilage repair studies (N = 55)
- Finished 3 months of training (N = 49)
- MRdGMERIC (N = 26)
MR dGEMRIC (delayed Gadolinium MRI of Cartilage) is previously found to correlate with proteoglycan content.
Methods

- MR dGEMRIC (delayed Gadolinium MRI of Cartilage) is previously found to correlate with proteoglycan content
- T2 mapping visualize the collagen type II organization
Surgical repair versus non-operative management

Improvements in knee function (Lysholm score and quadriceps muscle strength) can be obtained with 3 months of preoperative rehabilitation

Preoperative exercise is a valuable addition to or alternative to surgery for patients with femur condyle focal lesions: Almost 60% postponed surgery

(Aarøen et al. 2010)
Perhaps we can normalize PG and Collagen II by improved rehab!
How can we improve?

- Data on the natural history
  - Improvement over time after surgery is not necessarily a result of surgery - we need controlled studies
- Long term follow up in controlled studies - more good designed RCTs
- A non-industry controlled registry

- We are still on slippery ice
- But we are slowly getting a grip...
Scientific Evidence Base for Cartilage Injury and Repair in the Athlete

M.R. Steinwachs¹, L. Engebretsen², and R.H. Brophy³

Abstract

Soccer players and athletes in high-impact sports are frequently affected by knee injuries. Injuries to the anterior cruciate ligament and menisci are frequently observed in soccer players and may increase the risk of developing an articular cartilage lesion. In high-level athletes, the overall prevalence of knee articular cartilage lesions has been reported to be 36% to 38%. The treatment for athletic patients with articular cartilage lesions is often challenging because of the high demands placed on the repair tissue by impact sports. Cartilage defects in athletes can be treated with microfracture, osteochondral grafting, and autologous chondrocyte implantation. There is increasing scientific evidence for cartilage repair in athletes, with more extensive information available for microfracture and autologous chondrocyte implantation than for osteochondral grafting. The reported rates and times to return to sport at the preinjury level are variable in recreational players, with the best results seen in younger and high-level athletes. Better return to sport is consistently observed for all repair techniques with early cartilage repair. Besides minimizing sensorimotor deficits and addressing accompanying pathologies, the quality of the repair tissue may be a significant factor for the return to sport.
Figure 2. (A) Microfracture at the medial femur condyle. (B) Number of included study athletes who are able to return to sport of the preinjury level (RTSPL) after microfracture.
Figure 4. (A) Osteochondral grafting on the patella. (B) Number of included athletes who are able to return to sport of the preinjury level (RTSPL) after osteochondral grafting.

Figure 2. Treatment algorithm for the treatment of focal articular cartilage lesions in (professional) football players based on the best available evidence. (M)ACI = matrix autologous chondrocyte implantation.
Return to Sports after Articular Cartilage Repair in the Football (Soccer) Player

Table 1. Return to Play Overview

<table>
<thead>
<tr>
<th></th>
<th>MF</th>
<th>ACI</th>
<th>OAT</th>
<th>Allograft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return rate</td>
<td>68%</td>
<td>74%</td>
<td>91%</td>
<td>84%</td>
</tr>
<tr>
<td>Same level return</td>
<td>67%</td>
<td>71%</td>
<td>70%</td>
<td>60%</td>
</tr>
<tr>
<td>Time to return, mo</td>
<td>8 (6-18)</td>
<td>17 (10-36)</td>
<td>7 (4-9)</td>
<td>N/A</td>
</tr>
<tr>
<td>Durability (&gt;3 y)</td>
<td>56%</td>
<td>77%</td>
<td>72%</td>
<td>N/A</td>
</tr>
<tr>
<td>Decreasing function</td>
<td>42%</td>
<td>0%</td>
<td>20%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note: MF = microfracture; ACI = autologous chondrocyte implantation; OAT = osteochondral autograft transfer; N/A = no data available.

Collecting data from the literature, special focus was placed on data in football athletes with information on return rate, timing of return, level of postoperative competition, and the ability to compete in the sport over time. Results: Twenty studies describing 1,469 athletes including football players with articular cartilage injury were reviewed. Average return to sport was 79% without a significant difference in return rate or postoperative level of play between cartilage repair techniques. Time to return varied between 7 to 17 months, with the longest time for autologous chondrocyte transplantation (ACI). Advanced sport-specific rehabilitation was able to reduce recovery time. Durability of results was best after ACI, with up to 96% continued sport participation after more than 3 years. Player age, time between injury and treatment, competitive level, defect size, and repair tissue morphology affected the ability to return to play. Sports participation after cartilage repair generally promoted joint restoration and functional recovery. Conclusions: Articular cartilage repair allows for a high rate of return to high-impact sports including football, often at the preinjury competitive level. The time of return and durability can be variable and depend on repair technique and athlete-specific factors. Advanced, sport-specific rehabilitation can facilitate return to football.
### Table 1. Options for Treatment of Cartilage Injury

<table>
<thead>
<tr>
<th>Nonoperative interventions</th>
<th>Frontier surgical options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutraceuticals</td>
<td>New scaffolds</td>
</tr>
<tr>
<td>Viscosupplementation</td>
<td>Bone marrow aspirate concentrate</td>
</tr>
<tr>
<td>Platelet-rich plasma</td>
<td>Single-stage cell techniques</td>
</tr>
<tr>
<td>Pulsed electromagnetic fields</td>
<td>Chemical modification of marrow cells</td>
</tr>
<tr>
<td></td>
<td>Genetic modification of cells</td>
</tr>
</tbody>
</table>

**Figure 2.** (A) Minced juvenile cartilage, (B) postharvest histology (DeNovo), and (C) CAIS with staple in defect.
The challenges in osteoarthritis...
The Oslo Sports Trauma Research Center has been established at the Norwegian School of Sport Sciences through generous grants from the Royal Norwegian Ministry of Culture, the South-Eastern Norway Regional Health Authority, the International Olympic Committee, the Norwegian Olympic Committee & Confederation of Sport, and Norsk Tipping AS.