Autologous Chondrocyte Implantation



David A Parker FRACS

Advanced Course on Knee Surgery

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Declaration of Interest

The author has the following disclosures:

- editorial board of: AJSM, JISAKOS, AP-SMART Journal, OJSM
- hold shares in: Personalised Surgery, Ganymed Robotics
- received royalties from: Smith & Nephew
- done consulting work for: *Smith & Nephew*
- given paid presentations for: Arthrex, Smith & Nephew
- received institutional support from: *Smith & Nephew, Zimmer, Corin, Arthrex*



William Hunter 1718-83

"From Hippocrates down to the present age, we shall find, that an ulcerated cartilage is universally allowed to be a very troublesome disease; that it admits of a cure with more difficulty than a carious bone; and that, when destroyed, it is never recovered."

Hunter W. Of the structure and disease of articulating cartilages. Phil Trans. 1743;470-514.





History of Cartilage Repair

Evolution of Autologous Chondrocyte Implantation



History of ACI

- 1960 Chesterman & Smith described successful transplantation of isolated chondrocytes in rabbits
- 1980-Robert Salter –healing of full thickness defects in rabbits with continuous passive motion





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History of ACI

• 1987 – Brittberg and Petersen introduced ACI in Europe



First pilot study of ACI in humans Cultured chondrocytes injected under periosteal flap



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TREATMENT OF DEEP CARTILAGE DEFECTS IN THE KNEE WITH AUTOLOGOUS CHONDROCYTE TRANSPLANTATION

Mats Brittberg, M.D., Anders Lindahl, M.D., Ph.D., Anders Nilsson, M.D., Ph.D., Claes Ohlsson, M.D., Ph.D., Olle Isaksson, M.D., Ph.D., and Lars Peterson, M.D., Ph.D.









Evolution of ACI

- <u>First generation</u> --- Autologous chondrocytes harvested from cartilage biopsy and cultured
- Cells are implanted under a periosteal flap sutured with absorbable sutures
- Periosteal cambium cells release growth factors and promote chondrocyte maturation
- Modification --- Use of fibrin glue to seal the periosteal patch.





Evolution of ACI

- <u>Second generation</u> Injecting cultured chondrocytes under membrane of Type I or Type II collagen-avoided harvesting periosteal flap
- <u>Third generation</u> Cells embedded in extracellular matrix or temporary scaffold designed to induce cell growth and in-vitro maturation
 - Technically easier
 - Uncontained defects
- P-ACI ACI using periosteal membrane
- C-ACI ACI using collagen membrane
- MACI Matrix-induced autologous chondrocyte implantation



Chondral Grafting – ACI / MACI



Chondral Grafting – ACI / MACI







2 years post implant







Indications for ACI



Indications for ACI

• Focal full cartilage defects

Symptomatic Restore surface \rightarrow ?reduce risk osteoarthritis

• Outerbridge/ICRS III and IV lesions

Symptomatic: pain, stiffness, mechanical symptoms

• Secondary treatment after previous failed surgery

Microfracture, debridement, abrasion arthroplasty



Questions

- Does ACI work?
- Is it as effective as alternatives?
- What does it cost?









Literature: Results of ACI

Comparative Studies



P-ACI vs C-ACI

• Gooding et al:

- Level II randomized trial
- At 2 years follow up no difference noted
- Higher incidence of complication in P-ACI group as multiple patients required revision surgery for periosteal hypertrophy or delamination

Samuelson and Brown

- Level II cost effectiveness study
- C-ACI was more cost effective that P-ACI



MACI vs P-ACI/C-ACI

- Zeifang *et al* No statistical difference in scores at 2 years between MACI and P-ACI
- Bartlett *et al* Level II randomized study, MACI vs C-ACI . No significant difference in any outcome scores between two groups.



ACI vs Mfx

Treatment of Articular Cartilage Lesions of the Knee by Microfracture or Autologous Chondrocyte Implantation: A Systematic Review

CrossMark 2015

Sam Oussedik, B.Sc., F.R.C.S., Konstantinos Tsitskaris, M.R.C.S., and David Parker, M.B.B.S., B.Med.Sci., F.R.A.C.S.

• All studies showed clinical improvement with either technique

• Mfx

- Effective in smaller lesions
- More fibrocartilage production
- ACI
 - Likely more hyaline-like tissue produced
 - Effective in larger lesions
 - Periosteal technique \rightarrow more hypertrophy than membrane
 - MACI shown to be more effective than Mfx in lesions > 4cm²



ACI vs Mfx

Marrow Stimulation Has Relatively CME Inferior Patient-Reported Outcomes in Cartilage Restoration Surgery of the Knee

A Systematic Review and Meta-analysis of Randomized Controlled Trials

Torgom Abraamyan,*[†] MD, Alicia J. Johnson,[‡] MPH, Jack Wiedrick,[‡] MS, and Dennis C. Crawford,[†] MD, PhD *Investigation performed at Oregon Health & Science University, Portland, Oregon, USA*

- Systematic review and Meta-analysis (14 RCTs)
- No difference between Mfx and Mfx + Augment
- ACI / MACI significantly better improvements than Mfx
 - KOOS Sport & QOL
 - "May be a more appropriate treatment in younger and more active individuals"



ACI vs Mfx: ACI better

• Basad *et al* -- MACI more effective than MF for lesions > 4 cm²

- Saris *et al* KOOS scores, pain and quality of life were significantly better (< 0.05) in the ACI group compared to Microfracture
- Kon et al ACI group had significant improvement in the IKDC subjective and objective scores. Both groups resumed sporting activity at 2 years, activity decreased significantly in the Microfracture group at 5 years



ACI vs Mfx: Mfx better

- Knutsen et al Microfracture had greater improvement in SF-36 physical subscores after 2 years but no clinical or radiological difference at 5 years.
- In Microfracture group , smaller lesions < 4 $\rm cm^2$ had better Lysholm, VAS, and SF-36 physical scores than did those with larger defects
- No significant correlation between size and clinical outcomes in the ACI group.
- Overall younger and active patients had a better outcome than older and sedentary ones



ACI vs Osteochondral autografts

- Horas et al Randomised 20 patients each to P-ACI and Osteochondral autografts. Better improvement in Lysholm score in mosaicplasty group at one year but no significant difference at 2 years.
- Dozin *et al* No difference in Lysholm scores at 12 months
- Bentley et al Patients with ACI had superior Cincinnati Knee scores and Stanmore Bentley Functional rating at 1 and 10 years. Significantly high failure rate in mosaicplasty (55%) as compared to ACI(17%) at final follow up



Indications & Factors Affecting Outcomes



Algorithm for Treatment of Focal Cartilage Defects of the Knee: Classic and New Procedures

Betina B. Hinckel¹, Dimitri Thomas², Evan E. Vellios³, Kyle John Hancock⁴, Jacob G. Calcei⁵, Seth L. Sherman⁶, Claire D. Eliasberg⁷, Tiago L. Fernandes⁸, Jack Farr⁹, Christian Lattermann¹⁰, and Andreas H. Gomoll⁷ 2021

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- Large lesions (>4cm²)
- OCA preferred over MACI in subchondral bone involvement
- MACI preferred in PFJ



Orthopaedics

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ACI in PFJ

Clinical and Radiological Outcomes at \geq 10-Year Follow-up After Matrix-induced Autologous Chondrocyte Implantation in the Patellofemoral Joint

Jay R. Ebert,*^{††} PhD, Sven Klinken,[§] MBBS, Michael Fallon,[§] MBBS, David J. Wood,^{II} BSC, MBBS, MS, and Gregory C. Janes,[¶] MBBS *Investigation performed at the University of Western Australia, Crawley, Western Australia, Australia*

- 95 patients \rightarrow 82 patients avge follow up 12 years
- 29 concomitant TTO
- Significant improvement in PROMs sustained over > 10 years
- 90% satisfied with improvements in pain
- 85% satisfied with improvements in sports
- No difference between patella and trochlea
- 4 patients graft failure on MRI
- 3 patients went on to TKR



PFJ vs TF

- 168 patients, 10 year follow up
- Clinical and MRI
- High satisfaction with pain relief, sustained
- 76% satisfaction with sports
- 22 patients graft failure
- Tibiofemoral better clinical outcomes vs PF
 - Similar MRI findings

10-Year Prospective Clinical and Radiological Evaluation After Matrix-Induced Autologous Chondrocyte Implantation and Comparison of Tibiofemoral and Patellofemoral Graft Outcomes

Jay R. Ebert,^{*†‡} PhD, Minghao Zheng,[§] MD, PhD, Michael Fallon,[∥] MBBS, David J. Wood,[§] BSC, MBBS, MS, and Gregory C. Janes,[¶] MBBS *Investigation performed at University of Western Australia, Crawley, Perth, Western Australia, Australia*



Factors affecting outcomes

• Age:

- Younger patients have a better outcome
 - Knutsen et al & Bartlett et al
- Duration of symptoms:
 - Patient with lesser duration of symptoms had a better outcome
 - Bartlett et al & Saris et al
- Size and location of defects:
 - Femur > PFJ
 - Initial result of ACI in lesions >4 cm² was better compared to microfracture but no difference at 5 years
 - Jungman et al





Factors affecting outcomes

Factors Influencing Long-term Outcomes After Matrix-Induced Autologous Chondrocyte Implantation

Long-term Results at 10 Years

Johannes Weishorn,* MD , Johanna Wiegand,* Severin Zietzschmann,* MD, Kevin-Arno Koch,* MD, Christoph Rehnitz,[†] MD, PhD, Tobias Renkawitz,* MD, Prof., Tilman Walker,* MD, PhD, and Yannic Bangert,*[‡] MD *Investigation performed at Heidelberg University Hospital, Ruprecht-Karls-University Heidelberg, Heidelberg, Germany*

- 103 patients at 8.1 year follow up
- Survival (revision for any reason) 97% at 10 years
- All PROMs significantly improved at final f/u and MRI stable
- Influencing factors
 - BMI (Optimal range 20 29)
 - Previous surgeries
 - Correlation between MRI and PROMs





Adolescents vs Adults

Favourable clinical outcomes and low revision rate after M-ACI in adolescents with immature cartilage compared to adult controls: Results at 10 years

Johannes Weishorn [©] | Johanna Wiegand | Kevin-Arno Koch [©] | Raphael Trefzer [©] | Tobias Renkawitz | Tilman Walker [©] | Yannic Bangert [©]

- Comparison of adolescents (<20yo) to adults (avge age 32)
- 54 Matched pairs
- Adolescents
 - significantly higher KOOS
 - More likely to achieve PASS at long term follow up
 - Lower revision rates
 - Overall similar short term but better longer term



Osteochondral Defects

Autologous bone grafting in combination with autologous chondrocyte implantation yields favourable outcomes in the treatment of osteochondral defects of the knee: A systematic literature review

Stephan Oehme [©] | Joost A. Burger | Sophie Krafzick | Benjamin Bartek | Tobias Winkler | Tobias Jung

2024

- Systematic review 18 studies
- Autologous bone grafting + ACI for osteochondral defects
- Significant improvement across all PROMs
- Failure 0 17% at avge followup 6 years
- Favourable histological results

KNEE



Impact of Previous Surgery

A Randomized Trial of Autologous Chondrocyte Implantation Versus Alternative Forms of Surgical Cartilage Management in Patients With a Failed Primary Treatment for Chondral or Osteochondral Defects in the Knee

Martyn Snow,* MSc , Lee Middleton, MSc, Samir Mehta, MSc, Andrew Roberts, DM, Richard Gray, PhD, James Richardson, MD, Jan Herman Kuiper, PhD, and ACTIVE Consortium Investigation performed at the Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, Shropshire, UK

- RCT 390 patients
- Ages 18 55; Assessed 5 years postop
- Failed one previous surgical procedure
- 4 types of ACI vs Alternative (debridement, Mfx, Augmented Mfx)
 - Mfx most popular "standard" treatment 50%
- No difference in PROMs
- Previous Mfx: detrimental effect on ACI outcome



Impact of Previous Surgery

Increased Failure Rate of Autologous Chondrocyte Implantation After Previous Treatment With Marrow Stimulation Techniques

Tom Minas,* MD, MS, Andreas H. Gomoll, MD, Ralf Rosenberger, MD, Ronald O. Royce, DO, and Tim Bryant, RN

From the Cartilage Repair Center, Department of Orthopaedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

- Minas et al Retrospective study of 321 patients treated with ACI, 26 % failure rate in patients with prior marrow stimulation compared with 8 % in controls
- Petska *et al* ACI as first line treatment vs ACI following failed MF
 25 % failure in the MF group and compared to 4 % in the control group
- Biant *et al* Moderately higher failure rate 29% in those treated surgically (mosaicplasty, MF) compared with ACI as index procedure 19%



Longer Term Follow Up

- 168 patients
- Age range 15 63yo
- Minimum 10 year followup
- Significant long term improvements PROMs
- MRI good in majority
- All cause reoperation 9%
- Progression to TKR 7.4% at range 10 17 yrs

Minimum 10-Year Outcomes of Matrix- CME Induced Autologous Chondrocyte Implantation in the Knee

A Systematic Review

Allen S. Wang,* MS (b, Christopher V. Nagelli,* MS, PhD, Abhinav Lamba,* BS, Daniël B.F. Saris,* MD, PhD, Aaron J. Krych,* MD , and Mario Hevesi,*[†] MD, PhD Investigation performed at Mayo Clinic, Rochester, Minnesota, USA





Rehabilitation: Weight bearing

An accelerated 6-week return to full weight bearing after matrix-induced autologous chondrocyte implantation results in good clinical outcomes to 5 years post-surgery

Jay R Ebert $^{1\ 2}$, Michael Fallon 3 , David J Wood 4 , Gregory C Janes 5

- Wondrasch et al:
 - Level 1 randomised trial
 - Early weight bearing is favourable following MACI
 - FWB by 6 weeks
- Ebert et al:
 - Randomised trial
 - 63 patients (31 accelerated, 32 delayed)
 - Accelerated weight bearing (6 week return to FWB)
 - No compromise to graft or outcomes





Summary of Literature

- Younger patients & shorter duration of symptoms better outcomes with MACI
- MACI is more effective for lesions > 4cm²
- MF is less effective for lesions > 4cm²
- MACI is equal or better than MF early and more so at 5 years
- Osteochondral allografts are similar to MACI at 1-2 years but three times failure rate at 10 years
- MACI, C-ASI and P-ASI give similar results
- More complications with P-ACI
- Significantly higher failure rate with MACI which follows prior microfracture
- Early weight bearing favoured



Personal Experience & Current Role of MACI



Where was MACI in my Practice?

- ~ 2005 2011
- Focal cartilage lesions, usually > 2cm diameter
- +/- Joint stabilization or realignment procedures
- Prior to that P-ACI













MACI in Australia

- Became very popular due to simplicity compared to earlier generations
- Reimbursed by insurance companies
- Cost: approx. \$A10,000 per case
- Expanded indication → Over used → increased failures
- Funding withdrawn by insurance companies
- Recent moves to reinstate with controls



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Previous Study: HTO alone vs HTO + MACI

- Medial compartment osteoarthritis
- Undergoing OWHTO
- 1st stage scope and biopsy
- 2nd stage HTO + MACI
- NWB 6 weeks
- KOOS
- MRI at 12 months

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Knee joint preservation with combined neutralising High Tibial Osteotomy (HTO) and Matrix-induced Autologous Chondrocyte Implantation (MACI) in younger patients with medial knee osteoarthritis: A case series with prospective clinical and MRI follow-up over 5 years

S. Bauer^{a,*}, R.J.K. Khan^a, J.R. Ebert^b, W.B. Robertson^a, W. Breidahl^c, T.R. Ackland^b, D.J. Wood^a

^a School of Surgery and Pathology (Orthopaedics), The University of Western Australia, Perth, Australia School of Sport Science, Exercise and Health, The University of Western Australia, Perth, Australia Perth Radiological (Unic, Subico, Perth, Western Australia, Australia)





Outcomes MACI and HTO

- 2 surgeons
- 24 combined MACI and navigated OWHTO
- 2009-2011
- Most are 14 years postop
- No clinically meaningful difference outcomes
 - KOOS Symptoms better in MACI
- MRI variable
- Additional expense not justified
- Revised 4 to TKA





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Current Role of MACI in my Practice

- Younger patients (<20)
- Isolated traumatic lesions
- > 2cm diameter (>3cm²)
- Subchondral plate intact
- Patient willing to:
 - Pay (public hospital possible)
 - Comply with rehab
- Alternatives
 - Simple debridement +/- drilling
 - Minced cartilage
 - OATS / Mosaicplasty





Articular Cartilage Restoration

- Remains the future Holy Grail
- Huge investment & even bigger potential return
- Little meaningful progress since initial days of ACI
- Long way to go
- Need for good independent research, responsible introduction, and evidence-based practice







Thank You









WELCOME See you in Munich!

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