Ivy Sports Medicine
Life is Movement

CMI®

Study Review

Studienzusammenfassung

COLLAGEN MENISCUS IMPLANT

Literature Review on Clinical Experience

The CMI® implant is a type I collagen-based meniscus implant designed to faciliate growth of new tissue to replace removed or missing meniscus tissue in the human knee.

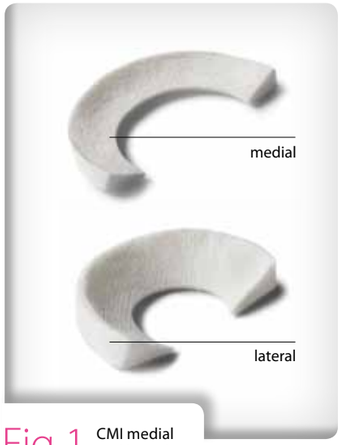

Fig. 1 CMI medial and lateral

The Collagen Meniscus Implant (CMI®) by Ivy Sports Medicine is an innovative treatment method designed for patients with irreparable meniscal injuries or prior loss of meniscus tissue. The CMI is:

- The first and only biologic implant for regrowth of new meniscus-like tissue
- A resorbable scaffold made out of highly purified bovine type I collagen
- Available for arthroscopic treatment of medial or lateral meniscus injuries
- Sizable to the respective defect
- Made from a material with excellent and proven biocompatibility

The CMI has been in clinical use since a first feasibility study started in 1993. Multicenter trials were started in the US and in Europe in 1997. In Europe, the CMI was approved for sale in early 2000 and then slowly introduced to the market. Numerous studies outside the multicenter trials have been performed and report on mid- to longer-term clinical experience. The purpose of this document is to provide a review of the published scientific literature to determine the effectiveness of the Collagen Meniscus Implant for improving clinical and functional outcomes and for generation of durable new tissue.

Search Method

The medical literature (PubMed and Cochrane Database up to September 2011) was searched using key words "Collagen Meniscus Implant" or "CMI collagen scaffold" to identify publications relevant to the study purpose. Included were publications in English or German on clinical results, i.e. on patient outcomes and assessment of the new tissue (reviews, in vitro experimental studies, and animal studies were excluded). Thirty-four (34) publications were identified (as of September 2011); 13 of these met the inclusion criteria. Two additional publications were identified from cross-references and were reviewed. For the lateral CMI, only abstracts have been published to date on the EU multicenter study, and the most recent one is included in this review.
Out of these 16 studies, the majority (13) are single centre case series with a limited number of patients. One study is a large level I, prospective randomized controlled multicenter trial, and two are prospective non-randomized controlled level II studies. The longest mean follow up (FU) available is 11 years.

Evolution of the Arthroscopic Surgical Technique

Over the years, the surgical technique for CMI has changed. In the late 1990's until about 2003, the implant was hydrated and then delivered into the joint with a metal cannula. The implant was fixed with an inside-out suture technique requiring a postero-medial skin incision for suture retrieval. In approximately 2002, all-inside suturing systems became available for meniscal repair. These systems were gradually being used for fixation of the CMI, despite the fact that initially the manufacturer did not recommend its use. With the introduction of the lateral CMI in early 2006, the implant was delivered into the joint dry using a delivery clamp and was attached to the host meniscus rim almost exclusively with all-inside sutures (primarily FastFix from Smith & Nephew Endoscopy).
It should be noted that the longer-term results (5 and 10 year FU) currently available for the medial CMI were all achieved with the smaller implant (7.5 mm wide) and the early more invasive inside-out suture fixation technique.

Results

1) Patient Characteristics (see Tab. 1)

- A total of 631 patients have participated in the 16 studies listed in Tab.1. Four hundred thirty-two (432) were treated with CMI (370 with medial CMI/62 with lateral CMI) and were followed for different time periods up to 12 years for the medial CMI and approx. 5 years for the lateral CMI.
- Patient age ranged from 14-69 years with a mean of means of 36 years. Patients treated with the lateral CMI were younger on average (approx. 28 years) than patients treated with the medial CMI (approx. 38 years) in the studies reviewed. More male than female patients were treated.
- In many studies concomitant surgeries such as ACL reconstruction (ACLR), microfracturing of adjacent cartilage, and/or osteotomy were performed, sometimes in 50% and more of the cases. ACLR was the most frequent concomitant procedure and was reported to have no effect on clinical outcomes or on tissue growth compared to isolated CMI procedures [1, 3, 5, 7].
- Follow up (FU) rate is defined as "patients available for final FU/patients treated initially". Overall FU rates ranged from 40% to 100%, calculated for studies with more than 2 patients (Tab. 1). In 10/12 studies FU rates were above 82%. In the 2 studies with low FU rates, Genovese et al. 2007 [8] could only perform 2 year Arthro-MRIs in 40% of the patients, and in the study of Linke et al. 2006 [9], not all patients had reached 2 years at final FU resulting in a 53% and 77% FU rate for the HTO and CMI+HTO patients, respectively.

2) Efficacy

a) Durable Improvement of Knee Function and Activity Levels after CMI Treatment

Different clinical scores have been used but in most studies Lysholm score as an indicator of knee function and Tegner activity score were assessed and are shown over time in Fig. 2 and Fig. 3.

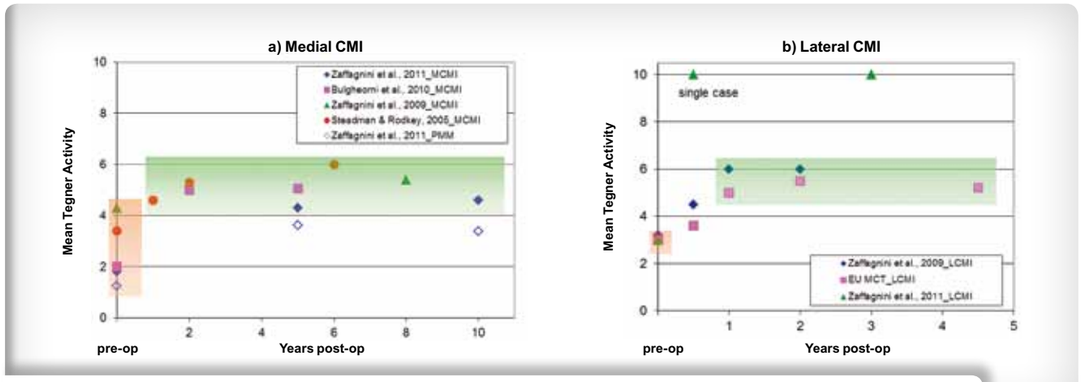

Fig. 2 Mean Tegner Activity pre-op (red shaded box) and post-op (green shaded box). Tegner activity improved significantly after CMI implantation and stayed improved from 1 to 10 years after medial CMI and for 5 years after lateral CMI, respectively.

Mean Tegner activity (Fig. 2) and Lysholm scores (Fig. 3) were significantly improved from pre-op to post-op both for medial and lateral CMI patients. Improvements were substantial and lasted over 5 and 10 years in lateral and medial CMI patients, respectively. Direct comparison between Lysholm or Tegner score of MCMI patients and PMM patients showed no significant differences at 5 and 10 years FU, but there was a trend to higher scores for MCMI patients. It was speculated that Lysholm score may not be sensitive enough to detect differences over this time period or differences may not be clinically relevant [3]. However, the Tegner Index - as a measure of how much lost activity after meniscus injury was regained – was significantly improved at 5 and 10 years in MCMI patients compared to PMM patients [3, 7]. It was argued that PMM patients reduce their activity levels in order to maintain pain and function at a level similar to the surgery he reached a Tegner score of 10, returned to professional soccer and has continued to play at that level for at least 3 years (Fig. 2b).

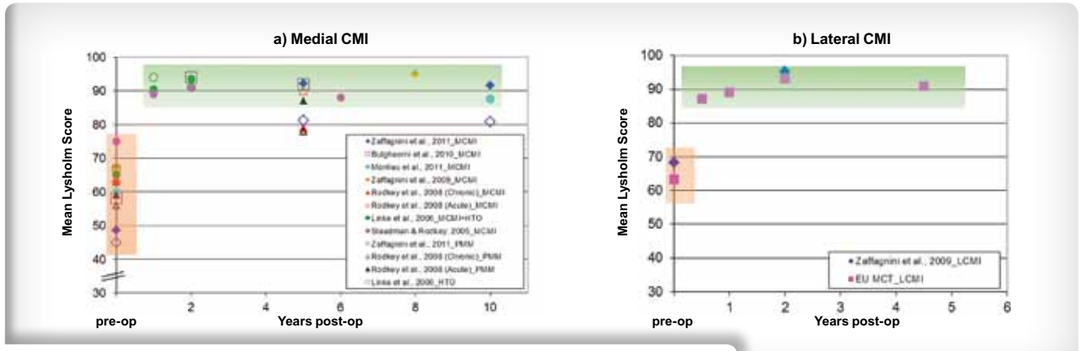

Fig. 3 Mean Lysholm scores were significantly improved post-op (green shaded box) compared to pre-op (red shaded box) and stayed improved in medial and lateral CMI patients.

b) Long-lasting Pain Relief After CMI

Post-op pain values were significantly reduced compared to pre-op in both medial and lateral CMI patients and stayed low over the FU period (Fig. 4). At 10 years post-op, pain in medial PMM patients increased compared to the level at 5 years post-op and was significantly higher than in CMI patients (Fig. 4a) [3].

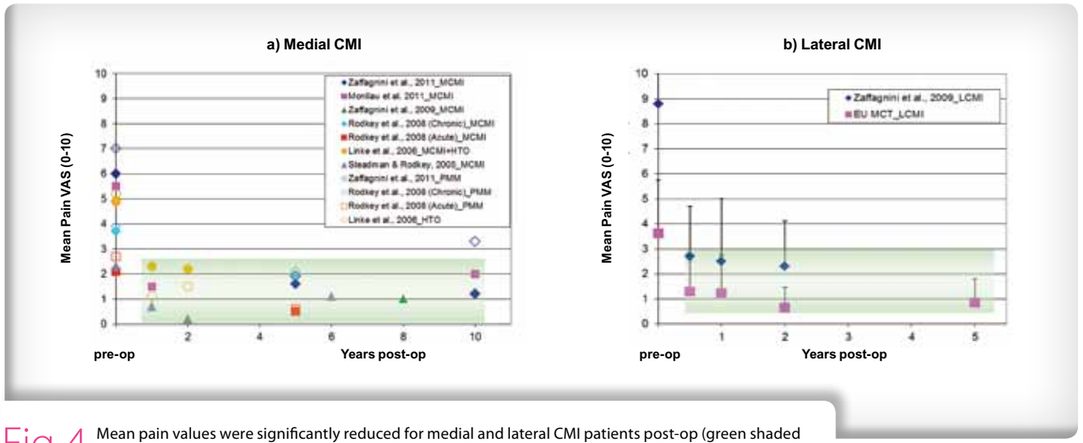

Fig. 4 Mean pain values were significantly reduced for medial and lateral CMI patients post-op (green shaded box) compared to pre-op. At 10 years, medial PMM patients had significantly increased pain (a).

Objective IKDC also showed significant improvement after CMI implantation compared to pre-op and at FU times of 2, 6 and 10 years no patient was worse compared to pre-op [3, 10, 13].
At 10 years, objective IKDC was also significantly better in MCMI patients (7A and 10B) compared to PMM patients (4B and 12C) starting from comparable pre-operative values [3].

c) Device-related Reoperation Rate Between 10-20%

Reoperation was defined as an additional unplanned surgical procedure on the involved meniscus as a result of disabling pain or mechanical symptoms associated with meniscus injury. Additional surgical procedures such as ACLR, biopsy harvesting for cartilage implantation, or metal removal after osteotomy may have been performed on the involved knee, but they are not considered reoperations since they did not concern the meniscus treated with CMI.
Device-related reoperations occurred in 20% [8] or less of the CMI patients (Tab. 1). Most studies reported no or a low percentage of device-related reoperations indicating that the CMI was a safe procedure. The reason for reoperation was mostly disabling pain due to persistent effusion/swelling which required additional treatment to resolve the problem such as debridement, osteotomy or an allograft implantation. In none of the studies was knee replacement required as a treatment for the serious complication. The study with the highest reoperation rate (20%) also had the highest percentage (53%) of concomitant surgeries inferring that these patients had very complex knee problems [8].
In the controlled study by Rodkey et al. 2008 [7], chronic CMI patients only required about half as many unplanned reoperations for treatment of pain as did the control (PMM) patients. In summary, 80% or more of the patients treated with CMI showed significantly improved knee function, symptoms, and activity levels.

d) Radiological Findings

X-ray assessment over time demonstrated no loss of joint space height and no degenerative changes of adjacent chondral surfaces after CMI implantation. Thus, joint space and chondral surfaces appeared preserved suggesting a chondroprotective effect of the implant [1, 3, 5, 10, 13, 16]. MRI assessment revealed that new tissue stayed in place and was well integrated with the host tissue. The volume of the new tissue compared to the normal meniscus was reduced which may be attributed to compressive forces acting during joint loading [8]. Signal intensity of the new tissue was hyperintense initially and progressively decreased over time indicating increasing maturity of the tissue over time (Fig. 5). While even at 5 to 10 years the MRI signal is not identical to a normal meniscus signal, the patient assessment from a clinical and radiological point of view is positive [1, 3, 5, 10]. Chondral surfaces were mostly unchanged from pre-op MRIs and degenerative changes of the cartilage did rarely occur over time. Genovese et al. 2007 [8] reported that subchondral bone marrow oedema resolved over time which may be an indication of stabilisation of the joint condition with ongoing maturation of the new meniscus-like tissue.

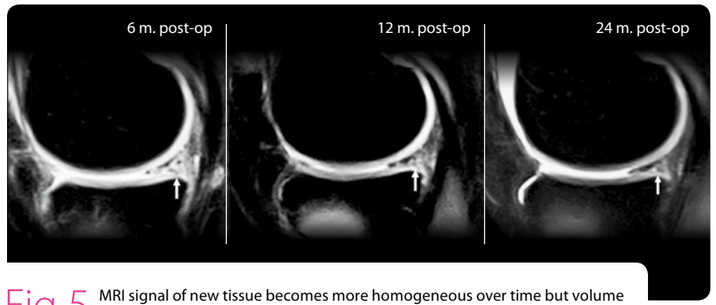

Fig. 5 MRI signal of new tissue becomes more homogeneous over time but volume is reduced or compressed. Courtesy of M. Ronga and E. Genovese, Varese (IT)

e) Relooks and Histology Show Durable Meniscus-like Tissue

Relook arthroscopy confirmed the presence of the new tissue and allowed visual evaluation of its appearance as well as evaluation of the chondral surfaces. The new tissue was well integrated with the host meniscus rim. In particular, the radial interfaces were stable upon probing (Fig. 6). The new tissue had different appearance in the various relooks. In some cases, sutures were clearly visible one year post-op and in others they seemed to be more embedded in connective tissue after the same period of time which is attributed to the biologic variability between patients. Several studies reported reduced size compared to the original meniscus similar to the MRI observations [5, 7, 8, 10]. A reduced meniscus size was reported not to have a clinical relevance. This finding may rather be attributed to compressive forces acting during joint loading as stated previously [8].
Chondral surfaces were unchanged compared to the time of surgery and no chondral damage or tissue hypertrophy due to the implant was observed. Defect filling was estimated during relook at one year post-op and reported to be approximately 70% [7, 13]. The new tissue sometimes exhibited fraying at the inner rim. Serial relook arthroscopy 5 years apart, confirmed that the new tissue was durable and remained functional during this time period [13].

Fig. 6 Example of a relook during HTO plate removal 1 year post medial CMI. Courtesy of S. Hinterwimmer, Munich (DE)

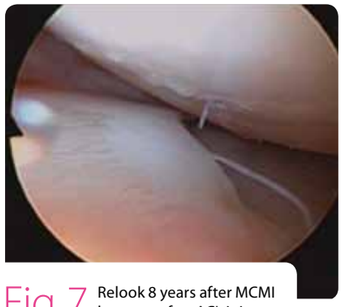

Fig. 7 Relook 8 years after MCMI because of an ACL injury while skiing. Courtesy of P. Niemeyer, Freiburg (DE)

Biopsies of the newly generated tissue were taken between 6 months and 5 years after implantation in 9 studies. Light microscopy of the biopsy specimen showed infiltration of connective tissue into the scaffold lacunae with cells resembling fibroblasts and with blood vessels [12, 14].
The more compressed appearance of the scaffold after implantation compared to the empty (dry) scaffold was thought to be likely a result of mechanical compaction due to compressive forces during joint loading [12]. Scanning electron microscopy (SEM) of the empty scaffold showed collagen fibrils with diameters ranging from approx. 70 to 440 nm with a bimodal distribution. SEM of 6 months specimens showed that newly synthesized collagen fibrils could be clearly distinguished from the implant collagen by their smaller diameter (up to 250 nm) [12]. Transmission electron microscopy (TEM) allowed detailed study of tissue ingrowth. The fibroblast-like cells showed intense metabolic activity. Pericellular filaments, the mesh-like pattern of the fibrillar network, and the lack of organization in chondrones demonstrated that the new hybrid tissue was still undergoing a maturation process which was also described by others [5, 7, 11, 12, 14].
While some authors reported no recognizable scaffold resorption at 6 months [12, 14], others reported about 75-90% at 1 year [7]. Bulgheroni et al. 2010 (5) reported implant remnants at 3 years post-op, but complete resorption in 5 year specimens as did Steadman and Rodkey, 2005 [13]. No inflammatory cells or phagocytes were present in any of the biopsy specimens evaluated at the different time points post implantation [5, 7, 11, 12, 13, 14, 16].

3) Safety

Use of the CMI has proven to be safe without damaging the chondral surfaces and without any other unanticipated negative effect such as tissue hypertrophy [1, 3, 5, 8, 11, 14]. The absence of phagocytes in the histology specimens confirmed biocompatibility of the collagen scaffold.

4) Conclusions

Relooks, histological and radiological findings all provide evidence that CMI induces and supports regeneration of meniscus-like tissue that remains in place and functional over more than 10 years. The clinical scores and low reoperation rates at longer FU periods demonstrate the clinical benefit that CMI offers to patients.

Although definitive proof that CMI implantation can prevent osteoarthritis is not yet available, several studies suggest a chondroprotective effect of the implant-generated new tissue. In the studies with the longest FU (10+ years), the authors stated that progression of OA was not observed in the medial compartment of most patients based on radiological assessment, and that joint status and joint space seemed preservedeven in patients with previous meniscectomy (i.e. chronic patients) [1, 3, 10]. This finding led the authors to suggest that the CMI appears to provide a chondroprotective effect and that CMI treated patients have a clear advantage in the long-run with improved symptoms and kneefunction and the possibility to stay active.

Tab. 1: Clinical studies with CMI: Patient Characteristics and Clinical Outcomes

Abbreviations: FU = follow up, MCMI=medial CMI; LCMI=lateral CMI, PMM=partial medial meniscectomy; ACLR= anterior cruciate ligament reconstruction, HTVO= hightibial valgus osteotomy, MFC=medial femoral condyle, IKDC score=International Knee Documentation Committee score; N.R. = not reported

Study	Evidence Level [a]	N (patients treated)	Mean age at surgery (range) (yrs)	Mean FU (yrs)	FU rate [b]	Concomitant surgery	Clinical Outcomes Diff. Pre-op mean to last FU mean (↑ = improved)	Relook (Tab.2)	Biopsy (Tab.2)	Reoperations of involved meniscus
Monllau, 2011 [1]	IV	25 MCMI	29.2 (18.3-48.2)	11.1 (10.1-12.5)	88% (22/25)	52% with ACLR	Lysholm ↑ by 28 | Pain ↑ by 35 | Patient satisfaction ↑	3	No	2/25 (8%) treated by allograft at 4 and 7 yrs post-op
Zaffagnini, 2011 [3]	II	18 MCMI	38 (24-60)	11.3 (10-12.6)	92% (33/36)	11% with ACLR 11% MFC microfracture	Tegner ↑ by 2.8 | Lysholm ↑ by 43 | Pain (VAS) ↑ by 48 | Obj. IKDC ↑	2	No	1/17 (6%) treated by HTO 7 yrs postop
		18 PMM	44 (28-60)	10.8 (10.2-12.1)		11% with ACLR 11% MFC microfracture	Tegner ↑ wby 2.1 | Lysholm ↑ by 36 | Pain (VAS) ↑ by 37 | Obj. IKDC ↑	2		2/16 (13%)
Zaffagnini, 2007 [10]	IV	8 MCMI (5 EU MCT)	31 (20-51)	6.8 (6-8)	100%	12.5% MFC microfracture	Pain ↑ | IKDC ↑ | CKRS ↑ | Self-assessment ↑	3	No	None
Bulgheroni, 2010 [5]	IV	34 MCMI	39 (22-58)	5 (5-6.3)	82% (28/34) 6 excluded	41% (32% with ACLR, 6% HTO, 3% microfracturing)	Tegner ↑ by 3.1 | Lysholm ↑ by 34	8	Yes	3/28 (11%) due to severe pain, treatment N.R.
Zaffagnini, 2009 [6]	IV	30 MCMI	44.8 at FU (28-67)	8.1	100%	N.R.	Tegner ↑ by 1.1 | Lysholm ↑ by 28 | Pain ↑ by 40	No	No	None
		12 LCMI	29.6 at FU (16-40)	1.7	100%	N.R.	Tegner ↑ by 2.8 | Lysholm ↑ by 27 | Pain ↑ by 65	No	No	None
Steadman, 2005 [13]	IV	8 MCMI	40 (24-49)	5.8 (5.5-6.3)	100%	None	Tegner ↑ by 2.6 | Lysholm ↑ by 13 | Pain (VAS) ↑ by 12 | IKDC ↑	8	Yes	None
Rodkey, 1999 [15]	IV	8 MCMI same patients as in [13]	40 (24-49)	2	100%	None	Tegner ↑ by 1.9 | Lysholm ↑ by 16 | Pain (VAS) ↑ by 21 | IKDC ↑	8 (+1)	Yes	None
Rodkey, 2008 [7]	I	160 MCMI 151 PMM	Acute: 40 Chronic: 38.5	4.9 (1.3-7.7)	96%	Total 27% with ACLR CMI: 29% with ACLR PMM: 25% with ACLR	Lysholm ↑ by 27 (acute) and by 19 (chronic) | Patient satisfaction ↑ Pain ↑	141	Yes	CMI group: 12/160 (7.5%) PMM group: 18/151 (11.9%)
Monllau, 2010 [4]	IV	49 LCMI	30.5 (14.7-54.7)	3.8 (2.8-4.4)	88% at 2 years	49% (12% ACLR, 18% med. meniscus procedure, 18% microfracturing)	Tegner ↑ by 2.2 | Lysholm ↑ by 28 | Pain ↑ by 28 | Patient satisfaction ↑	5	No	3/49 (6.1%) due to severe pain/swelling at 4-18 m. post-op, treated with debridement
Zaffagnini, 2011 [2]	Single case IV	1 LCMI	24	3	N.A.	None	Tegner ↑ by 7 | Pain (VAS) ↑ (no pain) | Subj. IKDC ↑ by 32 | Obj. IKDC: A	No	No	None
Stone, 1997 [16]	IV	10 MCMI	39.3 (24-50)	3	90%	40% (20% ACLR, 20% ACL microfracturing)	Activity ↑ | Pain ↑ | Overall knee rating ↑	9	Yes	None
Genovese, 2007 [8]	IV	40 MCMI	Median 41 (23-58)	2	1y: 100% 2y: 40%	52.5% (40% ACLR, 5% microfracturing, 5% ACI, 2.5% VTO)	N.R.	12	Yes	8/40 (20%) from 8-24 m. due to persistent pain
Linke, 2006 [9]	II	30 MCMI+HTVO	41.8 at FU (19-68)	2	77%	50% with HTVO	Lysholm ↑ by 28 | IKDC ↑ | Subj. Pain ↑	23	N.R.	1/23 (4%) due to dislocation of CMI, CMI was removed
		30 HTVO	41.6 at FU (19-68)		53%		Lysholm ↑ by 24 | IKDC ↑ | Subj. Pain ↑			
Ronga, 2006 [11]	Single case IV	1 MCMI	40	2	N.A.	100% (ACLR and MACI on MFC 7.5 months post)	N.R.	1	Yes	None
Reguzzoni, 2005 [12]	IV	4 MCMI	38 (24-50)	0.5	100%	None	Tegner ↑ by 2.2 | Lysholm ↑ by 31.5 | No pain after CMI	4	Yes	None
Ronga, 2003 [14]	IV	2 MCMI	N.R.	1	N.A.	N.R.	N.R.	2	Yes	None

[a] Evidence levels defined according to JBJS [17]
[b] FU rate is defined as patients available for final FU/patients treated initially

Tab. 2: Clinical studies with CMI: Radiological and histologic findings

Abbreviations: FC= femoral condyle, TP= tibial plateau, K-L score = Kellgren-Lawrence score; OA=osteoarthritis, N.R. = not reported

Study	X-ray findings	MRI findings	Relooks	Biopsy	Progression of OA
Monllau, 2011 [1]	At 10 years: minimal or no joint line narrowing (Rosenberg view)	• At 10 years: reduced size of meniscus in all 19 cases with MRI • 21% with normal meniscus signal intensity, 64% with irregular signal, 15% (3) no recognizable implant.	3 during reoperations: almost completely resorbed implant	No	No progression of OA in most cases based on Xray -> chondroprotective effect of CMI suggested
Zaffagnini, 2011 [3]	At 10 years: less joint space narrowing side-to-side difference in MCMI group compared to PMM group. Medial joint space preserved in MCMI group	• At 10 years: 24% with normal meniscus signal, 64% with irregular signal, in 12% no recognizable implant. • Meniscus size reduced. • Chondral surfaces in MCMI group preserved (Yulish score improved)	2 during reoperation but no information on implant	No	No progression of OA based on Xray -> Joint space preserved in MCMI group over 10 years suggesting chondroprotective effect
Zaffagnini, 2007 [10]	At 6 years: cartilage and joint space preserved in 6/8 patients compared to pre-op. 2 patients had 1 mm decreased joint space height.	• At 6 years: 5/8 with irregular implant signal, 2 with normal signal but reduced implant size, 1 no recognizable implant signal • Tissue maturation in 4 patients, 3 remained unchanged and in 1 case implant disappeared	• At 2 yrs post-op in 3: In 2 new tissue confirmed but with reduced volume, in 1 minimal new tissue. • Chondral surfaces unchanged compared to time of surgery	No (patients did not consent)	Joint status preserved even in patients with previous meniscectomy -> degeneration appears delayed
Bulgheroni, 2010 [5]	At 5 years: no degenerative cartilage changes in 64%, mild changes in 32%, severe OA changes in 1 case (3.5%) (K-Lscore) no pre-op X-ray available for evaluation of progression	• At 5 years: meniscus size reduced in 71% (at 2 years in 61%) • MRI signal matures from 2 to 5 yrs but not normal at 5 yrs. • Subchondral bone edema on FC and TP persisted from 2-5 yrs. • 60% with normal chondral surfaces, unchanged from 2-5 yrs	• Total 8: 4 at 7 m. and 1 each at 12,18,36,60 m. post-op (2 for metal removal after HTO, 2 with new trauma, 1 for cartilage biopsy, 3 because of pain) • New tissue confirmed but reduced in size • Tissue well integrated and stable upon probing • No chondral damage	• Meniscus-like tissue with cells and vessels, continuous tissue maturation and scaffold resorption • Implant remnants visible at 3 yrs, completelx resorbed at 5 yrs • Absence of phagocytes confirms biocompatibility	No pre-op Xrays available for evaluation of progression of OA Based on MRI, chondroprotective effect suggested
Zaffagnini, 2009 [6]	N.R.	• At 10 years: MRI with good signal of new medial meniscus. • Chondral surfaces in medial compartment appeared preserved	No	No	Preservation of medial compartment cartilage over 10 years
	N.R.	N.R.	No	No	N/A
Steadman, 2005 [13] & Rodkey, 1999 [15]	At 2 and 5.8 years: joint space height unchanged. mechanical axis not migrated medially	• New tissue well integrated and matured from 2-5.8 yrs • Normal signal at 5.8 yrs • No degeneration of med. compartment chondral surfaces from 2-5.8 yrs	• 8 patients w. consecutive re-looks at approx. 1 y and 5.8 yrs • 1 patient with painful plica 32 m. post-op • At 5.8 yrs: new tissue well integrated, 69% defect filling (decreased from 77% at 1 year due to wear of central margin)	• 3 biopsies at 5.8 yrs: Presence of fibrocartilage with uniform matrix • No inflammatory cells or immune response • No matrix remnants observed	Serial relooks confirmed that new tissue stayed in place, was durable in active patients and appeared to protect chondral surfaces of medial compartment
Rodkey, 2008 [7]	N.R. because high variability throughout 16 sites	N.R.	• In 141 MCMI patients at 1 y per study design • Additional relooks between 1 and 5 years: 13 in CMI group, 20 in PMM group • New tissue well integrated, in some cases incomplete filling and inner rim fraying • On average 73% defect filling • Chondral surfaces unchanged + intact • No tissue hypertrophy	• At 1 year: new tissue was hybrid repair tissue, fribrochondrocytic matrix with cells • 10-25% scaffold remained • No severe inflammation or giant cell response at 1 year	CMI supports growth of biomechanically competent meniscus-like tissue that results in improved knee function over 5 years
Monllau 2010 [4]	N.R.	• At 2 years: no loss of joint space and no progression of degenerative changes • Irregular signal	5 between 4-18 m. due to excessive pain and swelling	No immunologic reaction confirmed	N/A
Zaffagnini, 2011 [2]	At 3 years: no signs of degenerative OA	• At 3 years: implant in place, not extruded. • Mixed signal with reduced size • Chondral surfaces improved, no cartilage thinning	None	None	Potential protective effect for cartilage of involved compartment
Stone, 1997 [16]	At 3 years: no change in joint space height	• Sequential MRIs indicate ongoing ingrowth and regeneration of tissue	• 3 at 3 m. and 6 at 6 m. per study design • At 6 m. new tissue similar to fibrous meniscus tissue	• Invasion of collagen and cells • No inflammatory cells or immune reaction • Large amount of scaffold left at 3 m. which resorbed at 6 m. • At 6 m. new tissue still immature	No change in joint space height for 3 yrs
Genovese, 2007 [8]	N.R.	• Implant shape and size similar to normal meniscus in 88% at 6 m., but only in 56% at 2 yrs • 1 implant resorbed • Progressive reduction in signal intensity but not normal at 2 yrs tissue maturation not completed • Subchondral bone marrow edema decreased from 8-2 patients • With Arthro MRI 2 new cases with chondral defects detected at 2 yrs	• 12 from 6-24 m. due to persistent pain (8), additional procedures (2 ACI, 1 VTO plate removal), and new trauma (1) • Progressive reduction in implant size confirmed, implant completely resorbed in 1 patient	Histology revealed no inflammatory processes	N/A
Linke, 2006 [9]]	N.R.	N.R.	23 relooks per study design from 8-18 months during plate removal: 8 cases (35%) with complete healing, 7 with partial healing, 7 with small fragments only, in 1 dislocated implant had to be removed	N.R.	N.R.
Ronga, 2006 [11]		• From 6 m. to 2 yrs no change in implant size, signal becomes more homogeneous • Good restoration of chondral surface	• 1 at 6 m. for cartilage harvest for MACI procedure • 1 at 7.5 m. for ACI because chondral lesion left untreated at index surgery • Implant healed to host tissue	• At 6 m. scaffold invasion by blood vessels an cells producing new collagen fibrils • No inflammatory reaction and no macrophages	N/A
Reguzzoni, 2005 [12]	No	No	• 4 at 6m. per study design • New tissue healed to host meniscus, 1 implant with small fragmentation • No synovitis or chondral damage	• Connective tissue and cells invade into scaffold, no recognizable implant resorption, absence of phagocytes • New collagen fibrils with smaller diameter, fibroblast like cells with high metabolic activity	N/A
Ronga, 2003 [14]	N.R.	• At 12 m. shape and dimension of new tissue unchanged but signal more homogenous than at 6 m	2 at 6 m. implant healed to host tissue and stable upon probing	• Connective tissue , cells and blood vessels invade scaffold, new collagen fibrils with small diameter • No phagocytes demonstrating biocompatibility of CMI • No scaffold resorption microscopically	CMI stimulates regeneration of meniscus-like tissue that may prevent degenerative changes after meniscectomy

Monllau et al., 2011 [1]

Purpose: To evaluate the clinical outcome of the medial Collagen Meniscus after a minimum of 10 years follow-up. It was hypothesized that patients would show a decrease in pain and an improvement in functionality after CMI implantation and that this state could be maintained over 10 years with no progression or new development of degenerative knee joint disease.

Patients:

- 25 non-consecutive patients underwent CMI implantation between September 1997 and January 2000 (as part of the EU Multicentre Study).
- 20 male and 5 female patients
- Average age at surgery: 29.2 yrs (range, 18.3 – 48.2 yrs)
- 5 chronic post-meniscectomy cases (mean time meniscectomy to CMI surgery: 6.2 yrs) and 20 acute cases (mean time injury to CMI surgery: 3.5 yrs)
- 13 cases (52%) with concomitant primary ACLR
- CMI failure defined as implant-related infection or mechanical failure
- Patients were included in the European Multicentre Study of the medial CMI, the old surgical technique with inside-out sutures only and medial skin incision was used

FU time points: 1 year and minimum of 10 yrs post-op (mean 11.1 yrs, range 10.1-12.5 yrs)

Clinical Scores: Lysholm Score, pain (VAS), patient satisfaction

Radiology:

- X-rays: Rosenberg view for medial joint space narrowing according to Ahlbäck classification
- MRIs at pre-op, 1 year post (in 10) and at final FUP (in 19) -> Genovese scores to evaluate implant evolution (type 3 = MRI characteristics of normal meniscus, type 1 = resorbed and hyperintense signal)

Evidence Level: IV (Prospective, single centre case series)

Results:

- Lysholm scores improved significantly from 60 at pre-op to 90 at 1 year and 88 at final follow-up. Good and excellent results (i.e. > 84 points) were obtained for 83% of the patients despite the fact that 2 of the patients underwent meniscal allograft transplantation in the meantime.
- Pain (VAS) improved significantly from a mean of 55 pre-op to 20 points at final FUP. No differences were observed between the Lysholm and the VAS pain scores between 1 year and final FUP, indicating that the functional improvement was maintained over the 10 year time period.
- Patient satisfaction with regard to the procedure was 3.4 points of a maximum of 4.
  Concomitant ACLR did not influence the results compared to isolated CMI procedures.
- Radiologic evaluation using Ahlbäck grading showed no narrowing of the medial joint line in 11 patients (Ahlbäck grade 0) and some joint space narrowing in 12 patients (11 with Ahlbäck grade I and one with grade II) at final FUP. 4 patients progressed with 1 and 1 patient with 2 Ahlbäck grades over time whereas the other patients had the same Ahlbäck grade at final FUP compared to pre-op. Note: the Ahlbäck classification has variable reproducibility and low validity.
- MRI: at final FUP 4/19 (21%) had a type 3 "Genovese" signal, 12/19 (63%) had a type 2, and 3/19 (16%) had a type 1 signal. All cases showed less meniscus volume than expected at final FUP.
- Complications: no serious complications immediately post-op. At 6 months, 3 patients with slight and 4 with moderate effusions. Reoperations were necessary in 3 patients (12%):
  - 1 patient with repetitive knee effusions required a re-look arthroscopy at 4 years after CMI implantation. The implant was degenerated and not viable, and was replaced with a meniscal allograft.
  - 1 patient required a reoperation 14 months post-op in order to remove a Cyclops lesion that developed after the concomitant ACLR. The implant was almost completely resorbed but this fact had no clinical consequences at final FUP and was therefore classified as not device-related.
  - 1 patient complained of persistent pain and underwent an HTO and meniscal allograft 7 years after the CMI procedure. This patient was considered a protocol violation, because he had a 14° varus at the time of CMI placement that was not addressed because of the patient's involvement in sports. However, the CMI procedure allowed him to be mostly symptom free for a time period of almost 7 years.
  - Thus, 2 of the 3 cases that required revision surgery were classified as device-related failures (2/25 =8%).

Conclusions:

The available results suggest that the CMI provided significant pain relief and functional improvement for a time period of over 10 years. Although the implant generally diminished in size, the procedure proved to be safe with a low failure rate on a long-term basis. No development or progression of degenerative knee joint changes were observed in most cases.

Zaffagnini et al., 2011 [2]

Purpose: Report of a lateral collagen meniscus implanted in a symptomatic athlete desiring to return to high-level activity.

Patient:

- 1 male patient experiencing a lateral meniscus injury during a soccer match in March 2007, treated by partial meniscectomy with rehab for 2 months
- Continuous pain for 8 months, not able to play sports at pre-injury level
- Early 2008, lateral CMI implantation: intra-op 50% meniscus loss, implant length 40 mm
- New surgical technique with dry insertion and all-inside sutures
- Age at surgery: 24 yrs
- Strict rehabilitation for 6 months

FU time points: 6 months and 3 yrs post-op

Clinical Scores: Tegner activity score, pain (VAS), subjective and objective IKDC

Radiology:

- Weight-bearing X-rays at 3 yrs
- MRI at 3 yrs (Genovese score)
- Yulish scores for evaluation of chondral surfaces

Evidence Level: single case report

Results:

- Knee function improved rapidly such that the patient was able to play again in an official soccer match 10 months after CMI implantation. He continued to play 28 matches during the 2008-2009 season, 33 matches during the 2009-2010 season, and 21 in the 2010-2011 season with a professional soccer team.
- Tegner activity improved from 3 at pre-surgery to 10 at 6 months and at 3 years. Pain decreased to no pain at 3 years and the subjective IKDC improved from 68 at pre-op to 86 at 6 months and 100 (i.e. no limitation) at 3 years, objective IKDC was A at all time points.
- Radiologic evaluation: MRI showed normalization of the signal (increasing Genovese score) from 6 months to 3 years. At final follow up, the implant remains in place and does not appear extruded. Yulish score improved from baseline to 3 years and did not show thinning of the cartilage. Standard X-rays at 3 years showed no signs of degenerative arthritis.

Conclusions:

This case showed that in a symptomatic young patient with a failed lateral meniscectomy, partial replacement of lateral meniscal tissue with a CMI was a valid option to improve his knee function and enable return to high levels of sports activity.

Zaffagnini et al., 2011 [3]

Purpose: To evaluate the efficacy of the medial CMI (MCMI) compared to medial partial meniscectomy (PMM). Hypothesis: MCMI group will show superior clinical and radiographic outcomes compared to the PMM group at a minimum of 10 year FU.

Patients:

- 36 non-consecutive male patients underwent arthroscopic treatment for meniscal injuries between Oct. 1997 and Mar. 2000
- Average age at surgery: 40 yrs (24-60 yrs)
- 18 received a MCMI, 18 a PMM: assignment to MCMI or PMM not randomized, but patient choice
- All patients had comparable defect sizes
- All patients treated by same surgeon
- 50% acute and 50% chronic patients (with 1-3 prior surgeries)
- 4 (11%) patients with concomitant ACLR and 4 with microfracturing (2 in each group)
- 92% (33/36) of patients were available for final FU at 10 year
  (1 MCMI with tibial plateau fracture and 2 PMM patients did not complete FU evaluations)

FU time points: 5 and 10 yrs post-op; mean FU: 10.8 yrs (130 m.)

Clinical Scores: Lysholm score, Tegner activity score, pain (VAS), objective IKDC

Self-assessment: SF-36

Radiology:

- Weight-bearing X-rays

- MRI (at pre-op and 10-y)
- Yulish scores for evaluation of chondral surfaces

Evidence Level: II (Prospective, non-randomized, controlled study)

Results:

- Clinical scores (Pain, Lysholm, Tegner activity level) and SF-36 were significantly improved in the MCMI group at 5 year FU compared to pre-operative scores and this improvement was maintained up to the final 10 year FU.
- At 10 years, the MCMI group showed significantly lower pain scores (VAS) compared to the PMM group (1.2±0.9 vs. 3.3±1.8) and higher objective IKDC (7A and10B for MCMI, 4B and 12C for PMM) and Tegner scores (4.6±1 for MCMI, 3.4±1.3 for PMM). Differences in Lysholm score were not significant between the 2 groups at 10 years (91.6±8.9 for MCMI, 80.8±12.7 for PMM).
- Radiographic evaluation showed significantly less medial joint space narrowing side-to-side difference in the MCMI group compared to the PMM group. Moreover, the difference with the opposite knee was lower in MCMI group indicating that the medial joint space was preserved over the FU time period.
- MRI evaluation in the MCMI group (17 patients) revealed a mixed signal in 11, a normal signal in 4, and no recognizable signal in 2 cases. A progressive CMI signal maturation over time was not observed in this patient group.
- Evaluation of chondral surfaces by means of the Yulish score indicated a trend for a chodroprotective effect in the MCMI group compared to the PMM control group (difference not significant).
- Reoperations of the involved knee during the 10-y FU became necessary in 4 patients, in 2 (11.7%) patients with MCMI, in 2 (13%) with PMM due to swelling and pain symptoms that developed 7 years after index surgery. Swelling and pain in 1 MCMI patient was assumed device related (6%). Symptoms were successfully treated with debridement in 2 patients and HTO in the other 2 patients.
- MCMI survival rate at 10 years was approx. 85% and is comparable with that reported after meniscal repair

and superior to the 75% after meniscal allograft transplantation.

Conclusions:

Based on available results, 87% of patients benefited from implantation of the MCMI with improvements in pain, activity levels and radiological outcomes. Use of the scaffold for regrowth of meniscus appears to help patients to maintain activity levels while protecting the joint from pain and degeneration.

Bulgheroni et al., 2010 [5]

Purpose: Medium-term evaluation of clinical and radiological results in patients treated with CMI implantation for irreparable medial meniscus damage or post-meniscectomy pain. In particular, clinical improvements and its durability were evaluated as well as MRI evolution of the implant and the degenerative process of the knee.

Patients:

- 34 patients (25 men, 9 women) underwent arthroscopic medial CMI implantation between Jan. 2001 and Dec. 2003, average implant length 4.5 cm (2.6-6 cm)
- Average age at surgery: 39 yrs (22-58 yrs)
- 82% acute and 18% chronic (with prior meniscectomy) patients
- 14 (41%) patients with concomitant surgery: 11 with ACLR, 2 with HTO, 1 with microfracturing of medial FC for a chondral lesion of Outerbridge grade 3
- 28 available for FU at 5 years (82%)

FU time points: 2 and 5 years post-op, mean FU: 5-6.3 years

Clinical Scores: Lysholm score, Tegner activity score

Radiology:

- Weight-bearing X-rays at 5 years (Kellgren-Lawrence = K-L grade)
- MRI arthrography at 2 and 5 years
  - o for implant evaluation
  - o for evaluation of chondral surfaces using Yulish scores

Relooks: 8 patients with relook and biopsy at different post-op times

Evidence Level: IV (Prospective, single centre case series)

Results:

- 6 patients were excluded from study population: 4 refused intra-articular contrast fluid injection for arthro MRI, 1 not compliant with rehab with re-arthroscopy, 1 with re-injury and implant failure after 15 months.
- Average Lysholm and Tegner scores improved significantly from pre-op to 2 and 5 years post-operative. Lysholm scores improved from 58 pre-op to 94 at 2 and 92 at 5 years. Tegner scores improved from 2 pre-op to 5 at 2 and 5.1 at 5 years. Improvement was maintained through 5 years. Clinical scores appeared slightly better for acute than for chronic patients.
- Results did not differ for patients with an associated concomitant surgery compared to patients treated with CMI alone.
- Radiographic examination at 5 years showed no degenerative joint changes in 18 cases (K-L grade 0-1), grade 2-3 degenerative changes were evident in 9 cases and severe OA (K-L grade 4) was observed in 1 case. Pre-operative radiographs were not available for comparison, so evolution of joint degeneration could not be assessed

- **Arthro-MRI:**
  - o CMI meniscus smaller in size compared to normal meniscus in 61% at 2 years and in 71% at 5 years after implantation. CMI signal was hyperintense compared to a normal meniscus. Signal hyperintensity decreased over time but remained slightly abnormal even at 5 years.
  - o Appearance of the chondral surfaces was evaluated with the Yulish score. At 2 years after surgery 67% of the patients had a normal cartilage signal and at 5 year still 60% -> apparent chondroprotective effect at 5 years.
  - o Subchondral bone oedema was present 2 and 5 years after implantation in 10 patients in the femoral condyle and in 3 on the tibial plateau.

- 2 complications: 1 nerve injury during implant fixation and 1 non-compliance with rehab resulting in persistent knee swelling for 4 months requiring a re-arthroscopy that showed a completely dissolved implant.
- Relooks performed on 8 patients at different time points showed an implant with reduced size but the new tissue was well integrated with the surrounding native meniscus and stable upon probing. Reasons for relook: in 2 cases for HTO plate removal, in 1 for planned cartilage biopsy, 3 relooks for pain without associated trauma, 2 cases with re-injury -> 3 relooks were due to device-related problems (3/28 = 11%).

Conclusions:

Histology showed meniscus-like tissue with several cells and vessels. Progressive maturation of the regenerated tissue with resorption of the scaffold was observed. Some matrix fibers were still present at 3 years but not at 5 years after implantation. The absence of phagocytes and macrophages confirms the biocompatibility of CMI. The new tissue was irregular and appeared to mature over time, but even 5 years after implantation, the regenerated tissue remained different from normal meniscus.

Zaffagnini et al., 2009 [6]

Purpose: Evaluation of effectiveness of the lateral CMI after 13 years of good experience with medial CMI.
Report of interim results at this clinic. Description of evolution of surgical technique over the years.

Patients:

Medial CMI:

- 30 patients, average age at FU: 44.8 yrs (28-67 years)

Lateral CMI:

- 12 patients, average age at FU: 29.6 yrs (16-40 years)

FU time points:

- At 6 months, 1, 2, 5, 10 years (if possible)
- Medial CMI group: mean FU: 8.1 years
- Lateral CMI group: mean FU: 1.7 years

Clinical Scores: Lysholm score, Tegner activity score, pain (VAS), WOMAC knee examination form

Radiology:

- X-ray at 10 years in selected MCMI patients
- MRI at 10 years in selected MCMI patients

Evidence Level: IV (Prospective, single centre case series)

Results:

- There were no device-related complications during the respective FU time period for both the lateral and the medial CMI. All patients returned to activities of daily living without limitations within approx. 3 months.
- Functional assessment (based on Tegner activity level and Lysholm score) improved significantly in all patients from pre-op to last FU. For the medial CMI group Tegner improved from 4.3 (pre-op) to 5.4 (last FUP) and Lysholm improved from 67 (pre-op) to 95 (last FUP). For the lateral CMI group group Tegner improved from 3.2 (pre-op) to 6 (last FUP) and Lysholm improved from 68 (pre-op) to 95 (last FUP).
- Pain was greatly reduced after implantation: for the medial CMI group, VAS decreased from 5 (pre-op) to 1 (last FUP) and for the lateral CMI group VAS decreased from 9 to 2.
- Individual MRIs at 10 years post medial CMI implantation showed a good meniscus signal and no progressive degenerative changes of the chondral surfaces.

Rodkey et al., 2008 [7]

Purpose: Demonstrate that patients who received a CMI have improved clinical outcomes 2 years or more after implantation compared with their pre-operative status and compared with control patients with partial medial meniscectomy alone.

Patients:

- US multicentre trial conducted at 16 sites involving 26 investigators
- Patients with irreparable injury or prior loss of the medial meniscus, 18-60 years of age, neutral alignment, no grade IV chondral defects, and no PCL insufficiency were included.
- 311 patients underwent arthroscopic treatment, 160 received a CMI and 151 underwent a PMM (control group)
- 2 separate study arms with 157 acute (no prior surgery of involved meniscus) and 154 chronic (1-3 prior surgeries) patients
- Average patient age at surgery: acute group: 40 yrs, chronic group: 38.5 yrs
- 85 (27%) patients had a concomitant ACLR, 29% of CMI patients

FU time points: 1 year, mean FU: 4.9 years (range, 1.3-7.7 years)

Clinical Scores:

- Lysholm score, Tegner activity score, pain (VAS) at different activity levels, patient satisfaction
- Reoperation and survival rate through 5 years
- Status of cartilage surfaces with Outerbridge score

Radiology: • x-rays at 1 and 2 years post-op, but because of high variability at the different sites x-rays not analysed

1 Y Relook: In CMI patients only (FDA requirement):

- Amount of defect filling
- Histology of new tissue
- Assessment of chondral surfaces (Outerbridge)

Evidence Level: I (prospective, randomized, controlled trial)

Results:

1 year post-op:

- A 1 year relook was performed in 88% (141) of CMI patients. The CMI was successful in >90% of the patients and resulted in new tissue that appeared meniscus-like and was well integrated. CMI had resulted in a significant increase in total tissue surface area compared to PMM alone. The mean total tissue surface area had doubled compared to the one at index surgery (i.e. after prior meniscus surgery) in the chronic CMI group (73% vs. 37%). Inner rim fraying or partial resorption of the implant resulted in incomplete filling in some cases. Concomitant ACLR had no influence on tissue growth.
- The status of the chondral surfaces as assessed by the Outerbridge score did not change significantly during the first year in either the chronic or the acute CMI group. Mean Outerbridge scores were slightly lower in acute patients at the time of surgery compared to chronic patients. No tissue hypertrophy or chondral damage caused by CMI was observed.
- 1 year histology indicated that the CMI appears to provide a scaffold for the formation of meniscus-like fibrochondrocytic matrix. In nearly all cases there was evidence of infiltration of maturing connective tissue into the interstices of the CMI. At 1 year, about 10-25% of the scaffold remained based on visual estimates. No clinically relevant findings of severe inflammation or giant cell response were present in any of the biopsy specimens examined at 12 months. The new tissue consisted of a hybrid repair tissue.
- With new tissue ingrowth and matrix production considered as success, the CMI was successful in 97% of the chronic patients and in 70% of the acute patients.

5 year post-op:

- Tegner Index demonstrated that chronic CMI patients regained significantly more of their lost activity than chronic control patients 5 years after surgery (42% vs. 29%) thus returning more closely to their pre-injury activity levels. In the acute group, both CMI and PMM patients regained equal amounts of their lost activitylevel (on average 41%).
- CMI patients were more satisfied with their outcome than control patients in both the chronic and the acute group, but this was not significant.
- Pain scores, Lysholm scores and patient self-assessment improved between pre-operative and latest FU in all treatment groups but were similar regardless of treatment. Measures may not be sensitive enough to detect differences in a meniscus study or follow up time was not long enough for significant changes to develop.
- The rate of serious complications was similar in CMI and control patients (CMI: 7.5% vs. PMM: 7.3%). Although 7 of the 12 complications in the CMI group were classified as possibly or probably device-related (4.4%) it appears that implantation of the CMI does not lead to any more complications than did PMM.
- Reoperations: A total of 13 patients with CMI had a reoperation of the involved knee including 1 case with instability as the primary presenting symptom and ligament stabilization as the surgical treatment performed. This reoperation was not counted as possibly related to the involved meniscus resulting in 12 (7.5%) reoperations possibly related to failure of the implant in the CMI group. Similarly, 20 patients with PMM needed a reoperation with 2 ligament stabilizations not counted as PMM failure treatment, resulting in 18 (11.9%) reoperations after failed PMM. The chronic CMI patients had about half as many unplanned reoperations of the involved knee as did the controls (9.4% vs. 21.7%).
- At 5 years, the survival rate was significantly higher for chronic CMI patients (89%) compared to chronic PMM patients (74%) with reoperation as the end point. In the acute group there was no difference in reoperation and survival rates between treatment groups.

Conclusions:

Placement of CMI results in new, biomechanically competent meniscus-like tissue which enhances meniscal function as evidenced by improved clinical outcomes in patients with chronic meniscus injury. In the acute patient group, there was no difference between CMI and control patients. However, it has to be noted that in acutely injured patients the chondral surfaces are generally quite good and degenerative changes resulting from meniscectomy will occur to a much later point in time. The 5 year-FUP period was insufficient to observe such changes to occur in the acutely injured patients, but it was long enough to allow chronic CMI patients to achieve an activity level again that was comparable to acute patients.

Zaffagnini et al., 2007 [10]

Purpose: Prospectively evaluate subjective and objective results of the CMI at 6-8 years FUP.

Patients:

- 8 male patients underwent arthroscopic medial CMI placement between September 1997 and January 1999 (5 patients were included in EU MCT).
- Patients with irreparable injury or prior loss of the medial meniscus were treated, patients with grade IV chondral lesions and axial malalignment were excluded.
- Average patient age at surgery: 31 yrs (range: 20-51 yrs) and 39 at FUP (28-57 yrs)
- 3 acute cases without chondropathy, 5 chronic cases with prior subtotal meniscectomy combined with ACLR in 2 cases and 4 chronic cases with grade II chondral lesions.
- Concomitant procedure: 1 (12.5%) with microfracturing on MFC for grade III chondral lesion.
- Standard surgical technique with hydrated implant inserted and inside-out suturing including a medial skin incision.
- Average implant length inserted: 34 mm (range: 25-45mm).

FU time points: 1, 2, and 6-8 years, average FUP time: 6.8 yrs

Clinical Scores: Subjective Cincinnati Knee Rating System (CKRS), objective IKDC, pain (VAS), patient self- assessment (from IKDC)

Radiology:

- Standing x-rays and MRI pre-op, 2 and 6 yrs post-op
- Cartilage changes, joint space narrowing, implant signal changes

Relooks: 3 patients agreed to have a relook for evaluation of the new tissue. No patient agreed to biopsy.

Evidence Level: IV (Prospective, single centre case series)

Results:
- All 8 patients returned to daily activities without limitation 3 months after surgery.
- No complications related to the implant were reported.
- Functional assessment based on subjective CKRS improved in all 8 patients from pre-op to final FUP with a maximal score in 5 cases.
- Objective IKDC score improved in all cases from grade B (in 3 cases) and C (in 5 cases) to A (in 7 cases) and B (in 1). From 2 to 6 years FUP, 2 patients had a 10° loss of flexion which reduced their IKDC from grade A to B. At final FUP, 5 cases had an IKDC with grade A and 3 cases with grade B.
- All patients had reduced pain at 1 and 2 years post-op compared to pre-op, with 7 patients reporting no pain. In 4 cases the absence of pain remained up 6 years after surgery while in 4 cases a low level of pain was reported at final FUP.
- Knee function was normal or nearly normal for all patients based on self-assessment.
- Standing X-rays showed preserved cartilage and joint space in 6 cases. The 2 oldest patients at surgery showed a slight increase in OA 6 years after CMI with decreased joint space height of 1 mm (both were chronic post-meniscectomy patients).
- MRI evaluation showed a mixed implant signal in 5 cases, 2 cases had a normal signal with small implant size, while 1 patient had no recognizable implant signal. A tendency for maturation of the generated tissue appeared in 4 cases, while in 3 cases the MRI image remained similar at 2 and 6 years, and in 1 case the implant disappeared during this time period.
- 3 relooks at 2 years FUP revealed presence of new tissue in 2 cases, although with less volume than the original implant. In the third patient there was minimal new tissue. In 2 cases, the chondral surface was intact with no signs of degeneration, while in the 3rd case the grade III pre-operative cartilage lesions were unchanged.

Conclusions:
The implant appears to allow the patients to return to physical activity and sports without any adverse effects to the joint. X-ray findings similar to pre-operative conditions suggest a preservation of the joint status even in patients with previous meniscectomy.

Genovese et al., 2007 [8]

Purpose: Evaluate usefulness of MRI in the follow-up of patients treated with CMI to identify MRI patterns suitable for defining the evolution of the implant over time.

Patients:
- 40 patients (27 men, 13 woman) underwent arthroscopic medial CMI placement between March 2001 and June 2003.
- Median age at surgery: 41 years (range 23-58)
- 70% (28) acute patients, 30% (12) chronic patients (with prior partial meniscectomy)
- 21 (53%) with concomitant surgery (16 ACLR, 2 patella microfracturing, 2 ACI on medial femoral condyle, 1 VTO)

FU time points: 40 patients with regular MRI at 6 months and 1 year
16 patients with Arthro-MRI (after injection of intra-articular contrast medium) at 2 years

Radiology:
MRI performed for development of a new evaluation method using direct and indirect criteria.
- ***Direct criteria*** included morphology and signal intensity of CMI / meniscus complex (with type 1 to 3: type 3 corresponds to normal meniscus, type 1 corresponds to a totally resorbed or markedly hyperintense meniscus)
- ***Indirect criteria*** included condition of chondral surfaces, signs of bone marrow oedema at implant site, and associated synovial disorders

Relooks: 12 patients with relook and biopsy from 6-24 months after implantation. Relook due to persisting pain (in maximally 8 patients) or new joint trauma (in 1), autologous chondrocyte implantation (in 2), removal of VTO plate (in 1)

Evidence Level: IV (Prospective, single centre case series)

Results:

6 months FU (n=40):
- CMI shape and size normal (type 3) in 35 (87.5%) patients and type 2 in 5 (12.5%) patients
- Signal intensity markedly hyperintense (type 1) in 32 (80%) and slightly hyperintense (type 2) in 8 (20%) patients
- Interface between CMI and native meniscus could be identified in 27 patients
- 3 cases (7.5%) with chondral pathology of the medial femoral condyle (MFC)
- Subchondral bone marrow oedema detected in 8 patients (20%)
- 2 with pathological synovial reaction with marked intra-articular effusion

12 months FU (n=40):
- CMI shape and size normal (type 3) in 33 (82.5%) patients and type 2 in 7 patients
- Signal intensity markedly hyperintense in 14 (35%) and slightly hyperintense in 26 patients
- Interface between CMI and native meniscus identified in 19 patients
- 3 cases with MFC chondral lesions (7.5%)
- Subchondral bone oedema only in 3 patients (7.5%), in the other 5 cases it had completely regressed
- No case with pathological synovial reaction

24 months FU (n=16):
- CMI shape and size to be normal (type 3) in 9/16 (56%) patients and type 2 in 6/16 patients, no signal in 1 patient due to resorption
- Signal intensity hyperintense in 11/15 patients, normal signal intensity in 4/15, (no signal in 1 patient)
- Interface between CMI and native meniscus identified in 7 patients
- 2 cases with MFC chondral lesions (same as at 12m.) + 2 additional cases detected with arthro MRI (25%)
- Subchondral bone marrow oedema persisted in 2 patients (12.5%)
- No case with pathological synovial reaction

Morphology and size of the CMI were initially similar to normal meniscus in most patients, but with FU time implant size was reduced (88% normal at 6 months; 83% at 12 months; and only 56% normal at 24 months). This progressive size reduction was also confirmed by 2nd look arthroscopy (in 12 patients) and was attributed to implant height reduction due to compressive forces acting on the knee during motion. Progressive reduction in signal intensity over time: at 6 m. the signal was hyperintense in 80% and no implant had normal signal intensity at 6 or 12 months. At 2 years, only about 25% of patients showed signal intensity similar to normal meniscus indicating that the process of tissue maturation or regeneration was not completed. Arthroscopic and histologic findings showed that no inflammatory processes affected the implant site, confirming the safety and biocompatibility of the implant material.

Linke et al., 2006 [9]

Purpose: Detailed description of the initial surgical technique with delivery of a hydrated implant and inside-out fixation requiring a postero-medial skin incision.
Preliminary report of the results from patients with a high tibial valgus osteotomy (HTVO) combined with a CMI procedure compared to those from patients with a HTVO procedure alone.

Patients:
- 60 patients between 19-68 yrs with subtotal loss of medial meniscus and with varus morphotype were treated between January 2001 and May 2004: 30 patients received a concomitant CMI whereas the other 30 patients had an isolated HTO procedure.
- Average age at FUP for CMI+HTVO group: 41.8 yrs
- Average age at FUP for HTVO group: 41.6 yrs

FU time points: 3 months, 1 and 2 yrs post-op, not all patients reached 2 years!
Clinical Scores: Lysholm, IKDC self-assessment, subjective pain
Radiology: Not reported
Relook: 23 patients with relooks between 8 and 18 months during plate removal
Evidence Level: II (Prospective, randomized, controlled single centre study)

Results:
- Not all 30 patients of each group had reached the 2 year FU time point: in the CMI+HTVO group 23 patients were available with 2 year FU and in the group with HTVO alone only 16.
- Relook arthroscopy of 23 patients from 8-18 months post-op demonstrated different appearance of CMI regenerated tissue: in 8 patients the CMI was completely integrated into the host tissue; in another 7 patients integration into the host tissue was well but the posterior horn was partially frayed, whereas in 7 patients only small CMI fragments were seen and in 1 case the CMI was dislocated and had to be removed.
- Up to 1 year, the average Lysholm and IKDC score of the CMI+HTVO group was slightly lower than that of the HTVO patients. However for the patients available at 2 year FU, the Lysholm and IKDC scores were higher in the CMI+HTVO group compared to the HTVO group and were increased compared to the 1 year time point, whereas for the HTVO group the average Lysholm and IKDC values decreased compared to the 1 year time point.
- Device related reoperation: In 1 case the CMI had to be removed because of a dislocation (1/23 = 4.3%).

Conclusions: there were only slight and non-significant differences between the CMI+HTVO group and the HTVO group alone at 2 years post-op. However, not all patients had reached the 2 year FUP time point. Whether combination of HTVO with CMI can provide an improved chondro-protective effect compared to HTVO alone can only be determined after a longer FUP period.

Ronga et al., 2006 [11]

Purpose: Description of a 2-stage treatment performed on an athlete with a complex knee injury (simultaneous ACL rupture, irreparable meniscus tear and chondral lesion of the medial femoral condyle).
Patients:
- Male patient complaining of pain and anterior instability after sports trauma during soccer
- Age at surgery: 40 yrs
- 40 mm meniscal defect, 5 cm2 chondral lesion on medial femoral condyle
- CMI implantation and concomitant ACLR (patellar tendon graft)
- 6 months post-op: relook with biopsy and harvesting of cartilage cells for
- 7.5 months post-op: MACI of cartilage lesion on medial femoral condyle

FU time points: 6 months and 2 yrs post-op
Clinical Scores: ICRS score, CKRS, Lysholm, Tegner activity score, subjective IKDC form
Radiology: MRI at 6, 12, 24 months
Relook: At 6 months
Biopsy: At 6 months, light microscopy, SEM, TEM
Evidence Level: IV (single case report)

Results:
- Clinical scores were improved 2 years after CMI implantation and ACLR. ICRS score improved from severely abnormal at pre-op to nearly normal at 2 years; Lysholm score from 37 to 88 points, CKRS from 2 to 7 (of 10), Tegner from 2 to 6, and subjective IKDC from 31.1 to 81.5, respectively.
- 6 months after CMI implantation and ACLR the patient returned to normal daily activities, but still complained of pain because large chondral defect present at time of CMI implantation was not treated.
- MRI at 6 months showed an inhomogeneous signal and subchondral oedema at the site of chondral defect. MRI at 2 years showed no change in meniscus dimension with a more homogeneous signal.
- Relook at 6 months showed that the implant was healed to the capsule and the anterior meniscus horn.
- Light microscopy, SEM and TEM of biopsy tissue harvested at 6 months post-op showed scaffold invasion by blood vessels and cells producing new collagen fibrils. No macrophages and no inflammatory reaction were observed.

Conclusions:
In the reported case each lesion had to be addressed separately. Joint stability was first restored with CMI and ACLR, however this could not resolve the pain due to the chondral lesion. The cartilage repair procedure performed 7 months after CMI implantation appeared to provide pain relief and lead to the good clinical results 2 years after CMI and ACLR.

Steadman and Rodkey, 2005 [13]

Purpose: 5-6 year follow up of 8 patients from feasibility II study with medial CMI implant (see Rodkey et al.) to determine, a) if the newly generated tissue stayed within the original meniscus defect and remained functional, and b) if detrimental effects occurred due to the implant or new tissue over the 5 to 6 year period.
Patients:
- 8 male patients underwent arthroscopic medial CMI placement from Dec. 1995 to July 1996.
- Average age at surgery: 40 years (range, 24-49), at FUP: 46 years (range, 30-55)
- 7 patients with prior meniscectomy, 1 with acute irreparable meniscus bucket handle tear
- No concomitant intra-articular procedures performed

FU time points: 1 and 2 yrs, and at a mean FU of 5.8 years (range, 5.5 – 6.3 y), 100% FU rate
Clinical Scores: Pain, Lysholm, Tegner activity score, IKDC patient assessment
Radiology: X-ray and MRI at pre-op, 2 and 5.8 years
Relook: All patients with 2 serial relooks 4-5 years apart -> measurement of the amount of new tissue remaining over time.
Biopsy: Biopsy of the interface of native and new tissue in 3 patients at 5.5-6.3 yrs post-op
Evidence Level: IV (Prospective, single centre case series)

Results:
- No implant-related complications were reported during the 5 year follow-up period.
- Average Lysholm scores, Tegner scores and patient self-assessment improved significantly from pre-op to the last follow-up at 5.8 years. Although 2 patients had slightly decreased Lysholm score at 5.8 yrs compared to 2 yrs, no patient was worse (mean 88) at 5.8 years compared with the pre-op status (75). Tegner improved from 3.4 to 5.3 at 2 years and continued to improve to 6.0 at 5.8 yrs.
- Patient assessment (from IKDC) showed significant improvement at 5.8 and 2 years compared with pre-op. No patient was worse at the last FU compared with their pre-op status.
- Average pain improved from pre-op to post-op (23 to 11). One patient reported increased pain compared to pre-op because of a new injury approx. 5 years post CMI implantation.
- MRI indicated that the adjacent chondral surfaces of the medial compartment had not degenerated further since the placement of the implant approx. 6 years earlier. The newly generated tissue was well integrated and continued to mature between 2 and 5.8 years with the intra-substance signal intensity decreasing and becoming normal.
- The 2nd relook arthroscopy at 5.8 years post-op with direct measurement of the newly generated tissue revealed a 69% defect filling, which was a slight decrease from 77% at the 1 year relook. Nevertheless, the patients had much more meniscus tissue compared to the remnant of the index surgery. Moreover, relook arthroscopy confirmed the excellent integration of the new meniscus-like tissue with the host meniscus and demonstrated that the chondral surfaces of the medial compartment appeared protected and had not degenerated further. There was a slight reduction of the volume of the new tissue compared to the 1 y relook
- Histologic assessment of tissue biopsy specimens from 3 patients showed the presence of fibrocartilage with a uniform extracellular matrix. No matrix remnants were observed and no signs of infection, inflammation, or immune response in any biopsy specimen.

Conclusions:
The meniscus-like tissue that developed after placement of the CMI remained in place, maintained its structure and functioned over an average of 5.8 years. The serial relooks 4-5 years apart confirmed that the new tissue was durable, resembled normal meniscus tissue and appeared to protect the chondral surfaces of the medial compartment.

Rodkey et al., 1999 [15]

Purpose: Determine safety and potential efficacy of CMI (Phase II feasibility study). Implant geometry was altered to approximate closely the human medial meniscus shape compared to the Phase I feasibility study (Stone et al., 1997) but the implant material was the same. Specific study objectives were:
- Is CMI arthroscopically implantable?
- Do patients recover without complications?
- Does implant and new tissue remain mechanically stable?
- Can tissue regeneration be confirmed?

Patients:
- 8 male patients between 18 and 50 years underwent arthroscopic medial CMI placement from Dec. 1995 to July 1996.
- Average age at surgery: 40 years (range, 24-49)
- 7 patients with prior meniscectomy, 1 with acute irreparable meniscus bucket handle tear
- No concomitant intra-articular procedures performed, 2 patients with microfracturing of the MFC 8-12 w. before CMI implantation
- Average defect length 42.5 mm; average meniscus loss at surgery 62% (35-85%)

FU time points: 1 and 6 weeks, 3 m., 6 m., 1 and 2 yrs (range 24-32 m.)
Clinical Scores: Lysholm, Tegner activity score, self-assessment, pain (VAS 0-100) and blood collection
Radiology: X-ray and MRI at pre-op, 6 weeks, 3 m., 6m., 1 and 2 yrs
Relook: All patients agreed to relook surgery at 6 (6 patients) or 12 m. (2 patients) post-op
Biopsy: All patients agreed to biopsy of interface of native and new tissue at 6 or 12 m. post-op
Evidence Level: IV (Prospective, single centre case series)

Results:

- No complications related to the implant were observed, 1 patient with an additional relook due to excessive scar tissue formation was treated with debridement
- All patients returned to ADLs by 3 m. and were fully active by 6 months post-op.
- Lysholm scores improved from pre-op to 1 year in 7 patients and by 2 years in all 8 patients; Average Lysholm improved significantly from 75 at pre-op to 89 and 91 at 1 and 2 years post-op, respectively.
- Tegner activity score improved in 4 patients at 1 year and was unchanged compared to pre-op in the other 4. By 2 years, 7 patients had higher Tegner score and 1 had a lower score compared to pre-op. Average Tegner score improved significantly from 3.4 at index surgery to 4.6 and 5.3 at 1 and 2 years post-op, respectively.
- 4 patients had improved self-assessment at 1 year and 4 patients remained unchanged from pre-op (these patients had assessed their knees as nearly normal). By 2 years 5 patients had improved results compared to pre-op, and 3 with nearly normal knees remained unchanged.
- 7 patients had improved pain compared to pre-op at 1 and 2 years. One patient had worsened pain at 1 year compared to pre-op (when he was virtually pain free) but improved at 2 years. Average pain at pre-op was 23 and 7 and 2 at 1 and 2 years post-op (with 0 being no pain).
- Radiographs at 1 and 2 years revealed no progression of Fairbank changes and joint space changes compare to pre-op.
- 6 week MRI revealed slightly smaller size of the new tissue complex than the normal meniscus, the size did not change from 6 weeks through 1 year. There was consistently decreasing signal intensity with time postop suggesting ongoing maturation of the new tissue.
- Relook at 6 months and 1 year showed new tissue with variable degree of maturation in all patients. The new tissue had a stable interface with the host tissue and no significant fragmentation. There were no negative findings, no indication of wear particles, synovitis, inflammation or abrasion of articular cartilage. One patient had a painful plica 32 months post-op and returned for relook arthroscopy. Compared to the 6 months relook, the new tissue appeared to be of the same size and without fragmentation and the chondral surfaces were unchanged and without damage.
- Average defect filling was 77% (range of 40-100%) based on surgeons estimate.
- Histology of biopsy specimens showed that implants were invaded by cells similar to meniscus fibrochondrocytes and these cells were producing new matrix. No inflammatory cells other histologic evidence of immunologic reactions and no indication of any infection in any of the specimens was seen. The new tissue showed different degrees of maturity with the new matrix becoming dense with a fibrocartilaginous appearance. At 12 months remnants of implant material still present and maturation process seemed still ongoing.
- Immunology testing (ELISA assay) revealed no significant increase in antibodies to the implant and hypersensitivity to the implant material was not present.

Conclusions:

The findings confirmed that the CMI was arthroscopically implantable, was biocompatible and able to support new tissue regeneration. There was marked variation of the biologic response, with significantly more tissue regeneration in some patients. The new tissue seemed to function similar to normal meniscus tissue and seemed to protect the chondral surfaces up to 32 months after implant. placement.

Ronga et al., 2003 [14]

Purpose: Evaluation of the CMI by MRI, light microscopy and scanning electron microscopy (SEM) before and after implantation to asses tissue regeneration induced by the implant.
Patients: 2 patients
FU time points: 6 months and 1 year
Clinical Scores: Not assessed
Radiology: MRI at 6 and 12
Relook: At 6 months post-op
Biopsy: At 6 months post-op analysed with light microscopy and SEM
Evidence Level: IV (Prospective, single centre case series)

Results:

- Pre-op light microscopy of the dry scaffold showed a porous structure with lacunae (40-60 µm) and parallel connective bundles of 10-20 µm connected by smaller (5-10 µm) fibers. No cells detected in any section. SEM showed the scaffold surfaces with randomly oriented fibrillar network. Laminar planes made out of remnants of collagen fibrils (diameter 75-440 µm) randomly oriented and strictly packed next to each other.
- The relook at 6 months post-op demonstrated healing of the implant to the native meniscus rim. Implant appeared to be stable and consistent to fibrocartilage upon probing.
- Light microscopy of 6 m. biopsy specimen showed that specimen was inhabited by connective tissue with recognizable spindle-shaped or roundish cells and blood vessels. The presence of blood vessels indicate tissue viability. No phagocytomacrophagic cells were present which infers biocompatibility of the CMI.
  However, no sign of scaffold resorption was detected microscopically at 6 months.
- SEM of biopsy showed the multilamellar structure of CMI still evident but lacunae showed reduced width, i.e. scaffold appeared compressed. The scaffold collagen fibrils were surrounded by newly synthesized collagen fibrils with smaller and more uniform diameter (75-150 µm).
- MRI at 6 months demonstrated the presence of a tri-angular meniscus-like structure at the site of implant in both patients.
  On T2-weighted scans, signal intensity was very high with a non-homogeneous pattern
- MRI at 12 months showed an implant with shape and dimension unchanged, but the signal on T2-weighted images was more homogeneous and less intense compared to the 6 months images, more similar to normal meniscal fibrocartilage.

Conclusions:

The morphological findings demonstrate the capability of the CMI to stimulate regeneration of meniscus-like tissue and biocompatibility of the scaffold. The lacunae were populated with fibroblast-like cells synthesizing collagen fibrils; the newly synthesized fibrils were distinguishable from the scaffold collagen fibers for their smaller and more uniform diameter.

Reguzzoni et al., 2005 [12]

Purpose: Evaluate CMI by light microscopy, scanning electron microscopy (SEM), and transmission electron microscopy (TEM) before and after implantation to asses ultrastructure of newly formed tissue.
Patients:

- 4 patients
- Average age at surgery: 38 yrs (24-50)
- All with traumatic irreparable meniscus tear
- No concomitant injury, chondral surfaces intact

FU time points: 6 months
Clinical Scores: Lysholm score, Tegner activity scale
Radiology: None
Relook: At 6 months post-op approved by informed consent
Biopsy: At 6 months post-op analysed with light microscopy, SEM, TEM
Evidence Level: IV (Prospective, single centre case series)

Results:

- All patients returned to ADLs by 3 months and were fully active by 6 months post-op.
- No patient complained of pain or other symptoms in the operated knee but all patients approved to have a relook arthroscopy and biopsy at 6 months.
- Lysholm scores improved in all patients from an average pre-op score of 62.3 to 93.8 points at 6 months.
- Tegner activity scale improved in all patients from an average pre-op score of 2.3 to 4.5 at 6 months.
- 6 m. relook arthroscopy showed formation of meniscus-like tissue with healing of the implant to the residual meniscus in all patients. In 1 patient there was small fragmentation that did not require debridement. No signs of synovitis or damage of the chondral surfaces.
- Light microscopy of the 6 m. biopsy samples showed tissue invasion into the lacuna of the scaffold and no recognizable scaffold resorption. The scaffold appeared compacted likely due to the compressive forces during loading. The lacunae were filled by connective tissue with spindle-shaped or roundish cells surrounded by newly formed ECM and blood vessels.
  No phagocytes or macrophages were observed.
- SEM showed that the scaffold was composed of collagen fibrils with diameters ranging from 73 to 439 nm (mean 234 nm) with a bimodal distribution, however the newly synthesized fibrils had less uniform and smaller diameters ranging from 74 to 247 nm (mean 126 nm).
- TEM allowed detailed study of tissue ingrowth: whereas the empty CMI showed no cells or cellular debris, after implantation the lacunae

were filled by fibroblast-like cells. The cells showed intense metabolic activity demonstrated by the poorly condensed nuclear chromatin, the cytoplasmic organuli and the exocytosis vesicles, the presence of pseudopodia. These features are characteristic of fibroblast-like cells of unknown origin. The pericellular filaments, the mesh-like pattern of the fibrillar network, and the lack of organization in chondrones demonstrated that the tissue is still undergoing a maturation process.

Conclusions:
Morphological findings demonstrate that the CMI scaffold is still evident 6 m. post implantation
and does not elicit any inflammatory reaction. Histological and ultrastructural evidence of tissue ingrowth support
the hypothesis that CMI possesses tissue-conductive properties for generation of meniscus-like tissue.

Stone et al., 1997 [16]

Purpose: Feasibility I study: evaluation of safety and implantability of the scaffold as well as ability to support tissue ingrowth.
Patients:
• 10 patients (8 men, 2 women)
• Average age at surgery: 39.3 yrs (24-50 yrs)
• 4 patients with combined procedures (2 with ACLR, 2 with microfracturing of ACL)
FU time points: 3 years
Clinical Scores:
Activity score (1=strenuous activity, 5=inability to perform sports), pain (0=no pain, 3=severepain), overall knee rating, 1 leg hop-test
Radiology: MRI at 6 & 12 months, late MRIs done with intravenous gadolinium
Relook: 3 patients at 3 months post-op, in 6 patients at 6 months post-op
Biopsy: 3 patients at 3 months post-op, in 6 patients at 6 months post-op at time of relook
Evidence Level: IV (Prospective, single centre case series)

Results:
- 9 patients remained in the study for 36 months and one dropped out after 3 months (10%). Mild, transient effusions up to 2 weeks post-op were noted in 7 patients but resolved spontaneously afterwards.
- On a scale from 1(=strenuous activity) to 5(=inability to perform sports), the average activity score improved from 3 points before injury to 2.4 at 6 months, 2.2 at 12 months, 2.0 at 24 months and 1.9 points at 36 months post-op.
- Average pain improved from 2.2 points pre-op to 0.6 points at 36 months post-op (3=severe, 0=no pain).
- Overall knee rating on a scale from 1 to 3 (1=normal, 3=abnormal knee), improved from 3.0 at 12 months, to 2.0 at 24 months to 1.4 at 36 months. All 9 patients who completed the study stated that they hadimprovement and would have the procedure again.
- Standing x-ray demonstrated no major change in joint space height 3 years after CMI compared to joint height pre-operative.
- Sequential MRI revealed progressive changes over time, indicating ingrowth and regeneration of tissue. The new tissue exhibited increased signal intensity. Furthermore, the interface between new tissue and host tissue became less distinct over time and this was interpreted as a sign of ingrowth and regeneration of new tissue.
- Histology of 3 and 6 months biopsies showed progressive invasion of new collagen and cells resembling meniscal fibrochondrocytes. No inflammatory cells or signs of immunological reaction were noted. The 3 m. biopsy revealed a considerable amount of implant matrix with some new collagen but without organization. The new tissue was immature.
- Immunological evaluation revealed no apparent immune response and hypersensitivity to the CMI.
- 2/9 patients had an additional reoperation of the involved knee after the 1st relook: 1 patient after 21 months because of degeneration of the lateral joint space, the other patient after 19 months because of a re-injury of the involved meniscus in a fall while skiing. Both reoperations were not unrelated with the MCMI

Conclusions:
This initial clinical trial showed that the regenerated tissue seemed similar to meniscal cartilage. The CMI appeared to support regeneration even in the inner portions of the meniscus. The implant resorbed over time and appeared to be safe for the 3 years.

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