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

- Made from a material with excellent and proven biocompatibility
- Sizable to the respective defect
- Available for arthroscopic treatment of medial or lateral meniscus injuries
- A resorbable scaffold made out of highly purified bovine type I collagen
- Available for arthroscopic treatment of medial or lateral meniscus injuries
- Suitable to the respective defect
- Made from a material with excellent and proven biocompatibility

The CMI has been in clinical use since its 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 2013) 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 2013, 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 1 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 2001, 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 inside sutures (primarily FastF̈ 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.

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).
**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].

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 MCM 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 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 79% [7, 10]. 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].

**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 350 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 of 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].

**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 79% [7, 10]. 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].
Tab. 1: Clinical studies with CMI: Patient Characteristics and Clinical Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Evidence Level</th>
<th>N (patients treated)</th>
<th>Mean age at surgery (range yrs)</th>
<th>Mean FU (yrs)</th>
<th>FU rate (%)</th>
<th>Concomitant surgery</th>
<th>Clinical Outcomes</th>
<th>Retook (Tab.2)</th>
<th>Reoperations of involved meniscus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaffagni, 2011 [3]</td>
<td>II</td>
<td>18 CMI</td>
<td>28.5 (24.8-60)</td>
<td>11.3 (10.5-12.6)</td>
<td>50%</td>
<td>Tegner ±22.8</td>
<td>Pain ±28, Lysholm ±30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaffagni, 2007 [10]</td>
<td>IV</td>
<td>5 CMI (5 EU MCI)</td>
<td>24 (20-51)</td>
<td>10.8 (10.2-12.1)</td>
<td>40%</td>
<td>Tegner ±19.5</td>
<td>Pain ±19.5, IKDC ±32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulgheroni, 2010 [21]</td>
<td>IV</td>
<td>10 CMI</td>
<td>24 (22-48)</td>
<td>6.9 (5.6-8)</td>
<td>100%</td>
<td>Pain ±13</td>
<td>IKDC ±31, OKR ±2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaffagni, 2009 [6]</td>
<td>IV</td>
<td>8 CMI</td>
<td>24 (26-30)</td>
<td>1.9 (1.6-3.4)</td>
<td>40%</td>
<td>Tegner ±2.8</td>
<td>Pain ±10, None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siedman, 2005 [13]</td>
<td>IV</td>
<td>8 CMI</td>
<td>40 (24-49)</td>
<td>5.9 (5.6-8)</td>
<td>100%</td>
<td>Tegner ±5.5</td>
<td>Pain ±8.1, IKDC ±12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radley, 1999 [15]</td>
<td>IV</td>
<td>8 CMI (same patients as in [13])</td>
<td>40 (24-49)</td>
<td>2</td>
<td>100%</td>
<td>Tegner ±4.9</td>
<td>Pain ±20, IKDC ±20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radley, 2008 [17]</td>
<td>I</td>
<td>50 CMI</td>
<td>40 (34-49)</td>
<td>5</td>
<td>100%</td>
<td>Tegner ±2.1</td>
<td>Pain ±19.5, IKDC ±1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monkuu, 2010 [18]</td>
<td>IV</td>
<td>49 CMI</td>
<td>50.3 (45.7-54.7)</td>
<td>2.8 (2.8-4)</td>
<td>80%</td>
<td>Tegner ±5</td>
<td>Pain ±7, IKDC ±8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stone, 1997 [16]</td>
<td>IV</td>
<td>10 CMI</td>
<td>24 (24-50)</td>
<td>3</td>
<td>90%</td>
<td>Overall knee rating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gimeziane, 2007 [8]</td>
<td>IV</td>
<td>40 CMI</td>
<td>50.3 (45.7-54.7)</td>
<td>2</td>
<td>100%</td>
<td>N.R.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linke, 2006 [10]</td>
<td>III</td>
<td>30 CMI (HLVO)</td>
<td>41.6 at FU (9.6-48)</td>
<td>2</td>
<td>77%</td>
<td>Lysholm ±9.5</td>
<td>Pain ±28, IKDC ±10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reumann, 2005 [12]</td>
<td>IV</td>
<td>4 CMI</td>
<td>40 (24-50)</td>
<td>0.5</td>
<td>100%</td>
<td>Tegner ±2.2</td>
<td>Pain ±31.5, No pain after CMI</td>
<td></td>
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</tr>
</tbody>
</table>

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

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

Retooks, 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 preserved even 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 knee function and the possibility to stay active.

Abbreviations: FU = follow up, MCM = medial CMI, LCM = lateral CMI, PMM = partial medial meniscectomy; ACLP = anterior cruciate ligament reconstruction, HTVO = high tibial valgus osteotomy, MFC = medial femoral condyle; IKDC score = International Knee Documentation Committee score; N.R. = not reported.
<table>
<thead>
<tr>
<th>Study</th>
<th>X-ray findings</th>
<th>MRI findings</th>
<th>Relooks</th>
<th>Biopsy</th>
<th>Progression of OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montbrial, 2011 [1]</td>
<td>At 10 years: minimal or no joint line narrowing (Rosenberg view)</td>
<td>• At 10 years: reduced size of meniscus in all 19 cases with MRI • 21% with normal meniscus signal intensity, 64% with irregular signal, 15% (6) not recognizable implant.</td>
<td>3 during reoperations: almost completely resorbed implant</td>
<td>No</td>
<td>No progression of OA in most cases based on X-ray → chondroprotective effect of CMI suggested</td>
</tr>
<tr>
<td>Zaffagnini, 2011 [3]</td>
<td>At 10 years: less joint space narrowing side-to-side difference in MCM group compared to PMM group. Medial joint space preserved in MCM group</td>
<td>• At 10 years: 24% with normal meniscus signal, 64% with irregular signal, 12% non-recognizable implant. • Meniscus size reduced • Chondral surfaces in MCM group preserved (Kellgren-Lawrence score improved)</td>
<td>2 during reoperation but no information on implant</td>
<td>No</td>
<td>No progression of OA based on X-ray joint space preserved in MCM group over 10 years suggesting chondroprotective effect</td>
</tr>
<tr>
<td>Zaffagnini, 2007 [10]</td>
<td>At 6 years: cartilage and joint space preserved in 9/11 patients compared to pre-op. 2 patients had 1 mm decreased joint space height.</td>
<td>• At 6 years: 5/8 with irregular implant signal, 2 with normal signal but reduced implant size, 1 not recognizable implant signal • Tissue maturation in 4 patients, remained unchanged and in 1 case implant disappeared</td>
<td>• At 2 yrs post-op in 3/7 new tissue confirmed but with reduced volume in 1 minimal new tissue • Chondral surfaces unchanged compared to time of surgery</td>
<td>No (patients did not consent)</td>
<td>Joint status preserved even in patients with previous meniscectomy → degradation appears delayed</td>
</tr>
<tr>
<td>Bulgheroni, 2003 [9]</td>
<td>At 5 years: no degenerative cartilage changes in 64%, mild changes in 12%, severe OA changes in 1 case (3.2%) (K-L score) no pre-op X-ray available for evaluation of progression</td>
<td>• Total 8 at 4: 7 at 2 yrs, 1 each at 12,18,36,60. post-op (6 for metal removal after HTLD, 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 oil vessels and continuous tissue maturation and scaffold resorption • Implant remnants visible at 3 yrs, completely resorbed at 5 yrs • Absence of phagocytes confirms biocompatibility</td>
<td>N/A</td>
<td>No pre-op X-rays available for evaluation of progression of OA based on MRI, chondroprotective effect suggested</td>
<td></td>
</tr>
<tr>
<td>Zaffagnini, 2009 [4]</td>
<td>• At 10 years: MRI with good signal of new meniscal meniscus • Chondral surfaces in medial compartment appeared preserved</td>
<td>N.R.</td>
<td>No</td>
<td>Preservation of medial compartment cartilage over 10 years</td>
<td></td>
</tr>
<tr>
<td>Staudman, 2005 [13] &amp; Rodney, 1999 [15]</td>
<td>• At 2 and 5.8 years: joint space height unchanged, mechanical axis not migrated mutually • New tissue well integrated and matured from 2-5.6 yrs • Normal signal at 5.8 yrs • No degeneration of meniscal compartments • Chondral surfaces from 2-5.8 yrs</td>
<td>• Patient vs conservative re-takes 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, 64% defect filling (decreased from 77% at 1 year due to wear of central margin) • 3 lost cases at 5.8 yrs: Presence of fibrocartilage with uniform matrix • No inflammatory cells or immune response • No matrix remnants observed</td>
<td>N/A</td>
<td>Serial relooks confirmed that new tissue stayed in place, was durable in active patients and appeared to protect chondral surfaces of medial compartment</td>
<td></td>
</tr>
<tr>
<td>Rodney, 2006 [7]</td>
<td>N.R. because high variability throughout 16 sites</td>
<td>• In 1H: MCM patients at 1 y per study design • Additional relooks between 1 and 5 yrs. 15 in MCM group, 20 in PMM group • New tissue well integrated, in some cases incomplete filling and inner rim fraying • On average 77% defect filling • Chondral surfaces unchanged + intact • No tissue hypertrophy</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Mielke, 2010 [6]</td>
<td>• At 2 years: no loss of joint space and no progression of degenerative changes • Irregular signal</td>
<td>• At 2 yrs: Normal MRI • Chondral surfaces 3 months post-op, no cartilage thinning</td>
<td>5 between 4-18 m. due to excessive pain and swelling</td>
<td>No immunologic reaction confirmed</td>
<td>N/A</td>
</tr>
<tr>
<td>Zaffagnini, 2011 [2]</td>
<td>• At 3 years: implant in place, not resorbed • Mixed signal with reduced size • Chondral surfaces improved, no cartilage thinning</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>Potential protective effect for cartilage of involved compartment</td>
</tr>
<tr>
<td>Stone, 1997 [16]</td>
<td>• At 3 years: no change in joint space height • Sequential MRIs indicate ongoing ingrowth and regeneration of tissue</td>
<td>• 3 at 5 m. and 6 at 6 m. per study design • 4 at 6 m. new tissue similar to fibrocartilaginous tissue • Progressive reduction in implant size confirmed, implant completely resorbed in 1 patient</td>
<td>• Invasion of collagen and cells • No inflammatory cells or immune reaction • Large amount of scaffold left at 1 m. which resolved at 3 m. • At 6 m. no tissue still immature</td>
<td>No change in joint space height for 3 yrs</td>
<td></td>
</tr>
<tr>
<td>Genoveo, 2007 [8]</td>
<td>• 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 Arthrex MMR 2 new cases with chondral defects detected at 2 yrs</td>
<td>• 12 from 6-24 m. due to persistent pain (8), additional procedures (2 ACL, 1 VTO plate removal), and new trauma (1) • Progressive reduction in implant size confirmed, implant completely resorbed in 1 patient</td>
<td>Histology revealed no inflammatory processes</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Linke, 2006 [8]</td>
<td>N.R.</td>
<td>23 relooks per study design from 8-18 months during plate removal 8 cases (56%) with complete healing, 7 with partial healing, 7 with small fragments only, in 1 dislodged implant had to be removed</td>
<td>N.R.</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Roml, 2006 [11]</td>
<td>• From 6 m. to 2 yrs no change in implant size, signal becomes more homogeneous • Good restoration of chondral surface</td>
<td>• At 6 m. for cartilage harvest for MAC procedure • 1 at 75 m. for ACL because chondral lesion left untreated at index surgery • Implant healed to host tissue</td>
<td>At 6 m. scaffold invasion by blood vessels on cells producing new collagen fibres • No inflammatory reaction and no macrophages</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Requaero, 2005 [12]</td>
<td>• No</td>
<td>• At 4 yrs per-study design • New tissue healed to host meniscus, 1 implant with small fragmentation • No synovitis or chondral damage</td>
<td>• Connective tissue and cells invade into scaffold, no recognizable implant resorption, absence of phagocytes • New collagen fibres with smaller diameter, fibroblast-like cells with high metabolic activity</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Ronga, 2003 [14]</td>
<td>• At 12 m.: shape and dimension of new tissue unchanged but signal more homogeneous than at 6 m.</td>
<td>• At 6 m. implant healed to host tissue and stable upon probing</td>
<td>• Connective tissue, cells and blood vessels invade scaffold, new collagen fibres with small diameter • No phagocytes demonstrating biocompatibility of CMI • No scaffold resorption macroscopically</td>
<td>CMI stimulates regeneration of meniscus-like tissue that may prevent degenerative changes after meniscectomy</td>
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Monlau 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 meniscal 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 18) and at final FU (in 19) -> Genovese scores to evaluate implant evolution (type 3 = MRI characteristics of normal meniscus, type 1 = resorbed and hyperintense signal)

**Evidence Level:** N (Prospective, single centre case series)

**Results:**
- Lysholm scores improved significantly from 60 to 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 1 and one with grade 2) 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 4/7 (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. Resorptions 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 Gyclips 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 implant 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 2009, 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:** Lysholm 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 games during the 2008/2009 season, 33 games 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 at 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 (PMI). Hypothesis: MCMI group will show superior clinical and radiographic outcomes compared to the PMI group at a minimum of 10 year FU.

**Patients:**
- Average age at surgery: 40 yrs (24-60 yrs)
- 18 received a MCMI, 18 a PMI, assignment to MCMI or PMI 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 (7 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), subjective and objective IKDC

**Self-assessment:** SF-36

**Radiology:**
- Weight-bearing X-rays
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 KDC (7A and 10B for MCMI, 4B and 12C for PMM) and Tegner scores (4.6±1.1 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 chondroprotective effect in the MCMI group compared to the PMM control group (difference not significant).
- Reoperations of the involved knee during the 10 year FU became necessary in 4 patients, in 2 (11.7%) patients with MCMI and 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:
- 14 patients (25 men, 9 women) underwent arthroscopic medial CMI implantation between Jan. 2001 and Dec. 2003, average implant length 4.3 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 (Ketgreven-Lawrence = K-L grade)
- MRI arthrography at 2 and 5 years
- MRI for implant evaluation
- Evaluation of chondral surfaces using Yulish scores
- Relolooks: 8 patients with relolok 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), grade 2-3 degenerative changes were evident in 9 cases and severe OA (K-L grade 6) was observed in 1 case. Pre-operative radiographs were not available for comparison, so evolution of joint degeneration could not be assessed.

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:
- 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)
- Median 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 FU) and Lysholm improved from 67 (pre-op) to 95 (last FU). For the lateral CMI group, Tegner improved from 3.2 (pre-op) to 6 (last FU) and Lysholm improved from 68 (pre-op) to 95 (last FU).
- Pain was greatly reduced after implantation: for the medial CMI group, VAS decreased from 5 (pre-op) to 1 (last FU) and for the lateral CMI group VAS decreased from 9 to 2.
- Individual MRI’s 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.
- 311 patients underwent arthroscopic treatment, 160 received a CMI and 151 underwent 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: 48 yrs, chronic group: 38.5 yrs.
- 85 (27%) patients had a concomitant ACLR, 29% of CMI 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 activity level (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 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.
- 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 (32.5%) with microfracturing on MFC for grade II 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).

5 year FUP:
- VAS 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 that was comparable to acute patients.

Zaffagnini et al., 2007 [10]
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 2). From 2 to 6 years FUP, 2 patients had a 90% loss of flexion which reduced their IKDC from grade A to B. At final FUP, 3 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 to 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 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 II 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 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 hypointense 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 hypointense (type 1) in 32 (80%) and slightly hypointense (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 hypointense in 14 (35%) and slightly hypointense 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.

**Conclusions:**
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 hypointense 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. Arthoscopic and histologic findings showed that no inflammatory processes affected the implant site, confirming the safety and biosocompatibity 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 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.
- 10 patients received a concomitant CMH whereas the other 49 patients had an isolated HTVO 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.

**Relooks:** 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 frayred; 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 FU 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 FU 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 on the medial femoral condyle).

**Patients:**
- Male patient complaining of pain and anterior instability after sports trauma during soccer
- Age at surgery: 48 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 100 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 homogenous 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 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.

**Steadmam and Rodkey, 2005 [13]**

**Purpose:** 8-6 year follow up of 8 patients from feasibility study with mediolateral 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 FU, 6 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 3.8 years (range, 5.5 – 6.3 y), 100% FU rate

**Clinical Scores:** Pain, Lysholm, Tegner activity score, IKDC patient assessment

**Results:**
- 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 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 I feasibility study). Implant geometry was altered to approximate closely the human menisic 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 with the implantation?
- 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, 6, 9, and 2 years (range 24-92 m.)

**Clinical Scores:** Lysholm, Tegner activity score, subjective IKDC assessment, pain (VAS 0-100) and blood collection

**Radiology:** X-ray and MRI at pre-op, 6 weeks, 3, 6, 9, and 2 years

**Relook:** All patients agreed to relook surgery at 6 (5 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 in 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 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 compared to pre-op.
- 6 weeks 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 or 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 assess 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 months

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 phagocytes or macrophages were observed.
- No 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 fibrils 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 assess ultrastructure of newly formed tissue.

Patients: 4 patients

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 organeli and the ectosynthetic 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 chondrocytes demonstrated that the tissue is still undergoing a maturation process.

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

Stone et al., 1997 [16]

Purpose: Feasibility 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: 39.5 yrs (24-50 yrs)
- 4 patients with combined procedures (2 with ACL-R, 2 with microfracturing of ACL)

FU time points: 3 years

Clinical Scores:
Activity score (1=tremendous activity, 5= inability to perform sports), pain (0=no pain, 3=severe pain), 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 (tremendous activity) to 5 (inability to perform sports), the 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 5 (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 had improvement 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 month 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 CMI.

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.

References
Hersteller:
Ivy Sports Medicine
545 Penobscot Drive · Redwood City
CA 94063 · USA

Vertrieb:
Ivy Sports Medicine GmbH
Lochhamer Schlag 17
D-82166 Gräfelfing
Tel.: +49 (0)89 - 5 50 54 59-0
service@ivysportsmed.com

www.ivysportsmed.com

Kostenlose Service-Hotline
aus dem dt. Festnetz:
08 00 - 5 50 54 99