Cartilage
2016, Vol. 7(1) 29–38

DOI: 10.1177/1947603515600219
cart.sagepub.com
SAGE

Comparative Study of Collagen versus Synthetic-Based Meniscal Scaffolds in Treating Meniscal Deficiency in Young Active Population

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Abstract

*Purpose:*The aim of this study was to compare the effectiveness of 2 different meniscal scaffolds in treating patients with irreparable partial medial meniscal tear and patients complaining of pain in the medial compartment of the knee due to a previous partial medial meniscectomy. Based on previous studies, we hypothesized that both the scaffolds are effective in improving clinical outcomes in these patient populations. *Material and Methods*: Twenty-eight patients underwent collagen-based medial meniscus implantation (CMI-Menaflex) and 25 with a second-generation scaffold (Actifit). All patients were assessed with Lysholm, Tegner scale, and MRI evaluation—preoperatively, at 6 months, at 12 moths, and followed-up for a minimum of 2 years. Second look arthroscopy and concomitant biopsy were performed in 7 and 12 patients of CMI and Actifit groups, respectively. *Results*: The CMI group at final follow-up showed improvement in Lysholm score from 58.4 ± 17.3 to 94.5 ± 6.0, while the Actifit group showed improvement from 67.0 ± 15.7 to 90.3 ± 13.1; the improvement was statistically significant in both the groups but intergroup difference was not statistically significant ($P = 0.1061$). Tegner Activity Scale score improved in both the groups, but intergroup difference was not statistically significant ($P = 0.5918$). MRI evaluation showed *in situ* scaffold and no progression of degenerative arthritis in both the groups at final follow-up. Histological evaluation showed more fibrous tissue with blood vessels in the CMI group and the Actift group showed avascular cartilaginous features. *Conclusion*: Both the scaffolds are effective in improving patients' symptoms and joint function at short-term follow-up.

Keywords

scaffolds, meniscus, polarized light microscopy, meniscal injury, knee

Introduction

It is well known that deficiency of meniscal tissue can result in alteration of joint homeostasis and degenerative changes overtime.[1-4] In the past few years, meniscal scaffolds designed with tissue engineering techniques have been proposed to treat the meniscus-deficient knee to improve joint function and possibly delay arthritis. These scaffolds are structures designed with porous gaps of specific size and orientation, and its biomechanical characteristics and stiffness protect excess loading during normal joint function and also promote tissue regeneration.[5-8] Different types of scaffolds are currently under investigation, but to date only 2 meniscus implants are used to treat partial meniscus deficiencies: CMI-Menaflex (Ivy Sports Medicine, Montvale, NJ), composed of collagen and glycosaminoglycan; and Actifit (Orteq, London, UK), composed of polycaprolactone-polyurethane.

The CMI-Menaflex was proposed in 1992[9] and has been available for clinical use since 2000. It is composed of type I collagen isolated and purified from bovine Achilles tendon with added glycosaminoglycans and has a shape similar to the normal human meniscus. The CMI scaffold is arthroscopically implantable, biocompatible, and bioresorbable; ultrastructurally this scaffold is very porous. These features facilitate induction, proliferation, and differentiation of cellular elements within the scaffold, with

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consequent production of extracellular matrix to reproduce a meniscal-like tissue while the scaffold is gradually absorbed. *In vivo* studies in both animal and human models confirmed that CMI encourages proliferation of fibrochondrocytes and production of extracellular matrix.[9,10] In the recent years, several studies on collagen meniscus implants have showed significant clinical improvement and no progression of degenerative articular changes in most cases at mid-term and long-term follow-up.[11-15]

The Actifit is a synthetic and biodegradable scaffold composed of polycaprolactone-polyurethane and was introduced for clinical purposes for meniscal regeneration more recently. This structure seems to have better mechanical properties, as it is more resistant to surgical procedures, particularly to sutures, and to the loads during normal joint function. The increased absorption rate also allows full tissue regeneration. The scaffold's ultrastructure is characterized by 80% porosity and 20% low reabsorption rate polymer. Within the polymer there are softer polycaprolactone segments that constitute 80% of the polymer, and the rest of the 20% is a more rigid urethane. Degradation starts with hydrolysis of polycaprolactone segments that lasts up to 5 years, and polyurethane segments are removed by macrophages and giants cells or it may get integrated into the surrounding tissues.[15,16] A multicenter study showed that 81% of patients treated with the biodegradable polyurethane scaffold showed tissue ingrowth 3 months postoperatively, and biopsies at 12 months showed tissue infiltration with no sign of cell death or necrosis in 97% of the cases.[17] Several other clinical studies have also shown significant improvement of clinical scores without degenerative changes and scaffold-related adverse events at 2-year follow-up.[17-22]

The aim of this study was to compare the effectiveness of these different meniscal scaffolds in treating patients with irreparable partial medial meniscal lesions or in patients complaining painful medial compartment of the knee due to a previous partial medial meniscectomy. Based on previous individual studies, we hypothesized that both the scaffolds could be effective in improving symptoms and function in the above-mentioned patient groups.

Materials and Methods

Twenty-eight patients underwent collagen-based medial meniscus implantation (CMI-Menaflex), and 25 patients were operated using Actifit at our institution from 2001 to 2012. All patients were evaluated pre- and postoperatively with a minimum 2-year follow-up. Clinical evaluation was assessed with Lysholm score, Tegner scale preoperatively at 6 to 12 and 24 months after surgery, and radiological evaluation with MRI was done preoperatively and 2 years after surgery. Second look arthroscopy and concomitant biopsies were performed in 7 patients of the CMI group and 12 of the Actifit group at 4 to 45 months.

Our inclusion criteria were the following: skeletally mature male or female patients with irreparable medial meniscal tear or partial meniscus loss with intact rim and anterior and posterior horn (**Fig. 1**) who had normal axial alignment (mechanical tibiofemoral angle ≤3°) and stable joint. Patients with malalignment requiring osteotomy as well as patients requiring ligament repair for instability were been included and treated concomitantly.

The exclusion criteria were the following: advanced knee joint osteoarthritis, inflammatory arthropathy, and patients not willing to give consent for our follow-up and rehabilitation protocol.

CMI patients were treated between 2001 and 2002, and these patients were included in a previous study,[11] while Actifit surgeries were performed from 2009 to 2012 and all the patients were prospectively followed-up for a minimum of 2 years. All patients signed an informed consent to be involved in the study. The study has been approved by the Ethics Committee of the Ospedale di Circolo Fondazione Macchi, Varese, Italy (June 18, 2013; Protocol Number 0023851; Registered Clinical Trials 54/2013).

MRI Evaluation

Twenty-six patients in the CMI group and 21 patients in the Actifit group had a knee MRI preoperatively and 2 years after surgery. MRI evaluation was done in different centers according to a codified protocol as described in a previous study.[11]

The morphology and the signal intensity of the implant-regenerated tissue complex of the 2 scaffolds were evaluated with modified Genovese score.[23] Three patterns were identified and were classified from 1 to 3, with higher scores reflecting patterns more closely resembling those of the normal meniscus. The scaffold/residual meniscus complex was classified as grade 1, scaffold was totally reabsorbed; grade 2, scaffold appeared small with irregular-regular morphology; and grade 3, shape and size were identical to the ones of the normal meniscus. Regarding signal intensity, a markedly hyperintense scaffold was considered as grade 1, a slightly hyperintense was considered as grade 2, and if the scaffold signal intensity was isointense to the normal meniscus it was considered as grade 3. With regard to signal intensity, we divided the grade 2 of the Genovese classification into 2 subgroups: 2A and 2B depending on the degree (greater or lesser) of signal hyperintensity. The appearance of joint cartilage of the index compartment was evaluated using Yulish score, which was also used in other studies for evaluating the same.[11,14] According to this classification, cartilage lesions are defined as follows: grade 1, cartilage with normal contour ± abnormal signal; grade 2, superficial fraying and erosion or ulceration of <50% of thickness as demonstrated on MRI; grade 3, presence of partial thickness defect of >50% but <100%; grade 4, full thickness cartilage loss. Normal cartilage was classified as grade 0.

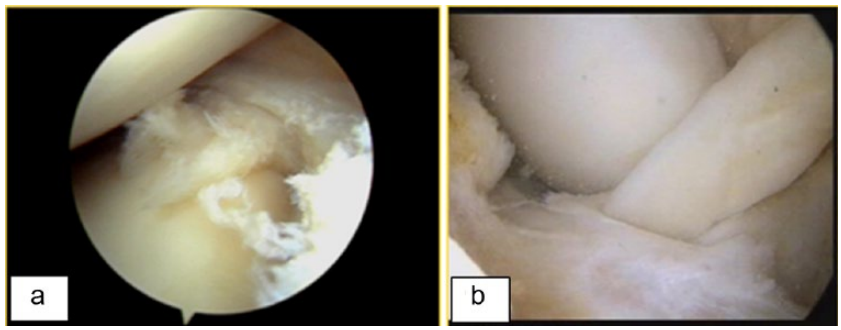

Figure 1. (**a**) Painful medial compartment, a chronic sequelae after previous medial partial meniscectomy. (**b**) Young patient with an irreparable bucket handle tear of the medial menisci.

Surgical Technique

Standard knee arthroscopy was performed through anterolateral and anteromedial portals. The native meniscus was trimmed back to the vascularized zone and the resultant defect was measured with a dedicated device. We provided extra blood supply by making puncture holes in the peripheral rim with a Steadman awl. Implant was prepared to the appropriate size and placed into the joint space; finally, it was firmly sutured to the native meniscus with inside-out technique or with a hybrid technique as needed. Few differences are present in the surgical technique of the implantation performed in different time period: in the first technique, CMI was introduced wet into the articulation using suture inside-out for the posterior horn with a posteromedial incision; in a second technique Actifit was introduced dry into the articulation using an all-inside suture (Fast-fix) for the posterior region.

Second Look Arthroscopy and Histological Evaluation

Seven cases of the CMI group and 11 cases of the Actifit group were subjected to second look. The biopsy was performed on the residual scaffold new tissue complex, and the center of the inner free edge of the scaffold was taken for histological analysis as suggested by Verdonk *et al*.[17] The histological evaluations of the CMI biopsies and the procedure to carry out the light microscopy analysis have been reported previously by Reguzzoni *et al*.,[7] and we adopted similar principles during our evaluation of these 2 scaffolds. All the specimens were dehydrated in ascending grades of ethanol and then embedded in paraffin. They were sectioned to 5-µm thickness with a Reichert Ultracut S ultratome (Leica, Vienna, Austria) and then stained with hematoxylin and eosin. Histological evaluation was performed with light microscopy (Nikon Eclipse E600 microscope, Nikon, Tokyo, Japan).[7] Furthermore, all the biopsy samples were also evaluated for any foreign body reaction in the synovium and in the pores of the implant, and scored according to an ordinal scale (grade 0 to grade 4) proposed by Van Tienen *et al*.[24]

Rehabilitation Protocol

Physical therapy was started from the first postoperative day: a knee brace was applied locked in full extension immediately after the surgery, and it was worn by the patient for 6 weeks. The patients were allowed to remove the brace 3 to 4 times a day to perform assisted passive motion exercises 0° to 30° for the first 2 weeks, 0° to 60° for the third week, 0° to 90° for the subsequent 2 weeks, and then were allowed free range of motion. Weight bearing was not allowed for the first 6 weeks; ambulation was permitted only with the aid of crutches. After 6 weeks, progressive weight bearing was started, eventually reaching complete weight bearing around the 10th week. Muscle strengthening was started from the second postoperative day with isometric exercises. All patients followed our rehabilitation protocol for 6 months until they returned to full unrestricted activity as tolerated. High-impact sports were allowed from the ninth month.

Statistical Analysis

The statistical analysis was performed using MedCalc (MedCalc software, Acacialaan 22, Ostend, Belgium). A priori power analysis was performed to establish the adequate sample size; a minimum of 23 patients for each group were required in order to detect a significant difference between CMI and Actifit of 10 ± 12 points at Lysholm score, with an effect size of 0.76, a statistical power of 0.80, and a probability level of 0.05.

Considering a 15% dropout rate, 28 patients for each group were included in the study.

Statistical comparison between the preoperative and postoperative follow-up parametric scores of both groups was performed using paired Student's *t*-test. The population study was tested for normal distribution before the *t*-test was applied. For differences between time points in Tegner level, the non parametric Wilcoxon test was used. For differences in categorical variables, the Pearson chi-square test was utilized. Comparison between the 2 groups and subgroups was performed using independent Student's *t*-test, Pearson chi-square test, or Mann–Whitney test depending on the variables.

Multiple regression analyses were performed to evaluate the whole case series using postoperative Lysholm score and Tegner Activity Scale as main outcomes. The regression analyses were performed in a backward fashion; in both models, independent variables considered were CMI or Actifit scaffold, acute or chronic pattern, age at surgery, isolated or combined procedure, male or female sex, and presence of chondral damage based on preoperative Yulish score I to IV. A logistic regression analysis was performed on the whole case series as well. Yulish score of grade I to IV was used as main outcome, while CMI or Actifit scaffold, acute or chronic pattern, age at surgery, isolated or combined procedure, and male or female sex were used as independent variables. Results are expressed using mean values ± standard deviation (SD) for parametric values, median ± interquartile range (IQR) for nonparametric values, and odds ratios and 95% confidence intervals (CIs) for logistic regression. Results were considered statistically significant at $P < 0.05$.

Results

Clinical evaluation

All 28 patients who underwent CMI were available at final follow-up (100%), while in the Actifit group 3 patients (11%) were lost at final follow-up. Both groups were comparable except for Tegner values, as the patients in the Actifit group, which included more chronic patients, were subjected to concomitant surgical procedure (**Table 1**).

The mean duration for scaffold implantation after meniscectomy in the Actifit group was 7.29 years (1-18 years), and for CMI group it was 8 years (2-16 years). The mean scaffold size during implantation in the Actifit group was 4.30 cm (1.8-6.5 cm), and in the CMI group it was 4.50 cm (2.1-6 cm).

The location of meniscectomy and details on concomitant procedures of both groups are presented in **Tables 3** and **2**, respectively.

The patients treated with CMI were older than those in the Actifit group; however, the difference was not statistically significant (CMI = 38.7 ± 9.7; Actifit = 34.4 ± 11.4; $P = 0.1569$). Though preoperative Lysholm and Tegner scored have higher values in the Actifit group, statistically significant difference was found only with Tegner scale, but these observations are completely random and probably are related to the relatively younger patients in the Actifit group compared with those in the CMI group. However, the difference in the Lysholm score and Tegner scale improvement, between the scaffolds, from preoperative to 6, 12, and 24 months ($P = 0.5918$, 0.4916, 0.5918) after surgery are not statistically significant (**Fig. 2**).

Analysis of individual groups showed statistically significant improvement in Lysholm and Tegner scores from preoperative to 12 months after surgery and at final follow-up (**Table 4**). The Lysholm score in the CMI group improved from 58.4 ± 17.3 to 94.5 ± 6.0 and in the Actifit group from 67.0 ± 15.7 to 90.3 ± 13.1 at final follow-up. The Tegner activity scale in the CMI group improved from 2 to 5 and in Actifit group from 4 to 5 at final follow-up. An intergroup analysis of Lysholm score ($P = 0.281$ and 0.106) and Tegner activity ($P = 0.491$ and 0.591) showed no significant statistical difference at 12 months and final follow-up, respectively (**Table 5**).

Table 1. Demographic Data of the 2 Groups.

Article I.	CMI ($n = 28$)	Actifit ($n = 25$)	*P* Value
Age[a]	38.7 ± 9.7	34.4 ± 11.4	$P = 0.1569$
Sex (male/female)	19/9	20/5	$P = 0.4909$
Knee involved (right/left)	20/8	13/12	$P = 0.2409$
Concomitant procedure	13	21	$P = 0.0105$
Meniscal lesion (acute/chronic)	22/6	7/18	$P = 0.0006$*
Surgical time[a] (minutes)	84±27	92±34	$P = 0.3254$

[a]Values expressed are mean ± standard deviation.
*Statistically significant.

Table 2. Type and Location of Meniscal Lesions in Both Groups.

	Actifit Group	CMI Group
Chronic lesions	18	6
Acute lesion	7	22
Posterior horn	5	8
Body	—	—
Body + Posterior horn	—	7
Bucket handle	2	7

Table 3. Concomitant Procedures in Both Groups.

Concomitant Procedures	Actifit Group[a]	CMI Group[a]
Tibial osteotomy	11	3
ACL reconstruction	9	11
Microfracture	3	1
Healing response	1	—
Suture	1	—

[a]Few patients have undergone >1 concomitant procedure.

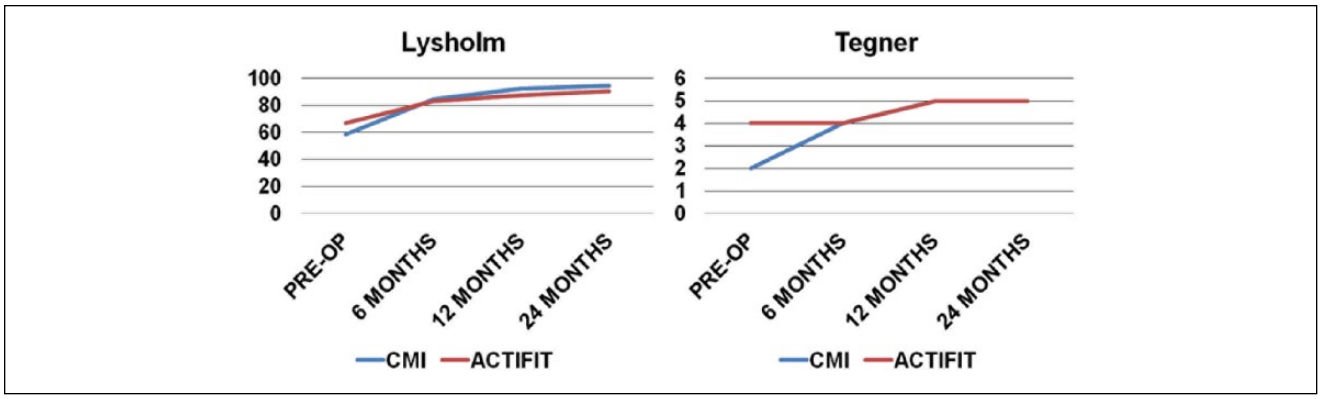

Figure 2. Linear graph representing Lysholm and Tegner scale improvement from preoperative up to 12 and 24 months after surgery in both groups of patients.

Table 4. Clinical Outcome Scores of the 2 Groups.

Group	Functional Outcome Scores	Preoperative Score	1-Year Follow-Up Score	Final Follow-Up Score	*P* Value; Preoperative vs. 1-Year Follow-Up	*P* Value; 1-Year Follow-Up vs. Final Follow-Up
CMI	Lysholm[a]	58.4 ± 17.3	92.5 ± 8.5	94.5 ± 6.0	*P* < 0.0001*	*P* = 0.1310
	Tegner	2	5	5	*P* < 0.0001*	*P* = 0.4015
Actifit	Lysholm[a]	67.0 ± 15.7	87.4 ± 13.0	90.3 ± 13.1	*P* < 0.0001*	*P* = 0.9460
	Tegner	4	4	5	*P* < 0.0001*	*P* = 0.1309

[a]Values expressed are mean ± standard deviation.
*Statistically significant.

Table 5. Intergroup Analysis of Clinical Outcome scores.

	CMI Group			Actifit Group			CMI Group vs. Actifit Group		
Functional Outcomes	Preoperative	1-Year Postoperative Follow-Up	Final Follow-up	Preoperative	1-Year Postoperative Follow-Up	Final Follow-up	*P* Value; Preoperative Score	*P* Value; 1-Year Follow-Up	*P* Value; Final Follow-Up
Lysholm[a]	58.4 ± 17.3	92.5 ± 8.5	94.5 ± 6.0	67.0 ± 15.7	87.4 ± 13.0	90.3 ± 13.1	*P* = 0.0775	*P* = 0.2814	*P* = 0.2395
Tegner	2	5	5	4	4	5	*P* < 0.0001*	*P* = 0.3927	*P* = 0.9341

[a]Values expressed are mean ± standard deviation.
*Statistically significant.

Multiple regression analysis showed that the type of implant did not affect Lysholm and Tegner values, but females and patients with concomitant procedure showed less improvement in Lysholm scores by 11 and 5.5 points, respectively, at final follow-up; chronic patients showed a decrease of Tegner score by 0.73 points at final follow-up.

Complications

Three complications were recorded in CMI group: neuro apraxia of infrapatellar branch of the saphenous nerve, which resolved after neurolysis; persistent synovitis; and superficial infection, which resolved after appropriate antibiotic therapy. In the Actifit group, 5 complications were recorded: joint stiffness, which resolved with arthroscopic release and manipulation under anesthesia, and 4 cases of synovitis, all of which resolved with anti-inflammatory therapy.

MRI Evaluation

MRI showed that the scaffolds in both groups were present *in situ* and were filled with new tissue but showed irregularity in shape and dimension of the scaffolds, while the signal intensity was higher in both the groups at final follow-up (**Fig. 3**). Except one CMI scaffold, which underwent complete resorption, all the remaining meniscal implants were partially resorbed in both the groups. The size of the remaining intact scaffold was reduced in 61% of CMI patients and 79% of Actifit patients. Scaffolds identical to native meniscus were observed in 39% and 21% of the patients in the CMI and Actifit groups, respectively.

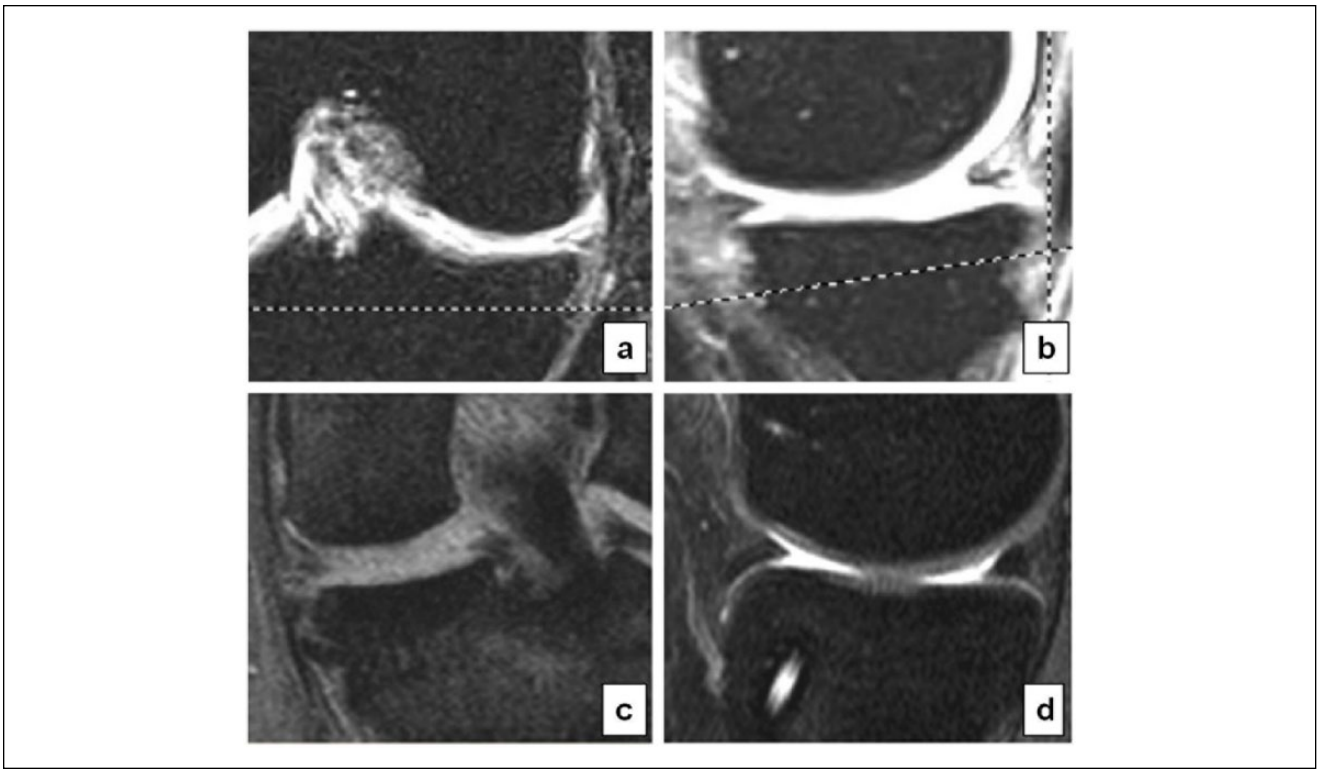

Figure 3. MRI of the 2 scaffolds with 2-year follow-up (CMI **a-b**, Actifit **c-d**); both the scaffolds are well positioned and well integrated. Both the scaffolds have irregular shape and different signals than the native meniscus.

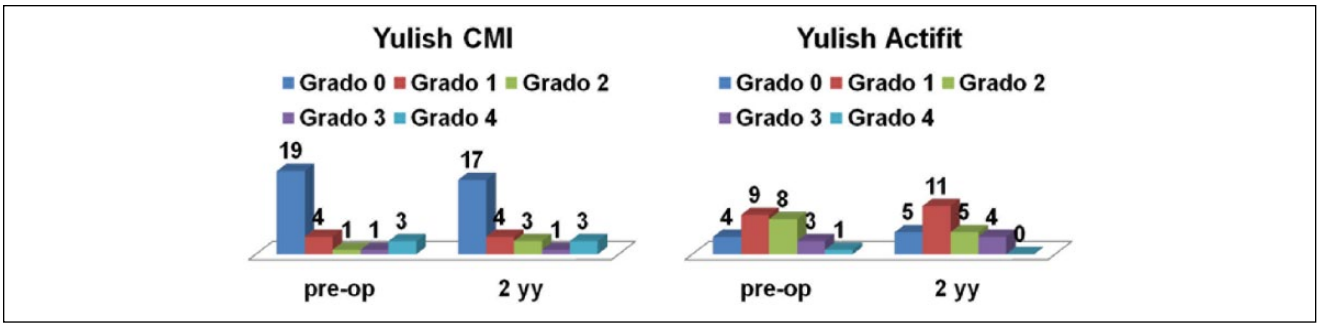

Figure 4. Bar graph representing Yulish scale in the CMI and Actifit groups both preoperatively and at final follow-up.

Regarding signal intensity, 54% and 68% of the patients showed grade 2A; 46% and 38% showed grade 2B signal intensity in the CMI and Actifit groups, respectively. However, we must underline that the composition of the 2 scaffolds is different and might affect MRI images.

Analysis of Yulish scale showed a greater degree of joint degeneration in the Actifit group both preoperatively and at final follow-up ($P = 0.0009$ and $P = 0.006$, respectively); however, no evolution of degenerative joint disease has been observed with the time (Actifit $P = 0.708$ and $P = 0.892$ CMI) (**Fig. 4**). Through logistic regression it was observed that chronic lesion patterns were associated with 4.312 increased risk of chondropathy (Yulish 1-4) at 2 years of follow-up (confidence interval = 1.096 to 16.955).

Second Look Arthroscopy

At arthroscopic evaluation an intact bare scaffold that was well integrated with surrounding tissue without any synovial tissue covering was seen in all except one case from the CMI group (**Fig. 5**). One patient from the CMI group who had persistent synovitis had complete scaffold resorption. The size of the scaffolds appeared to shrink over time and the margins appear frayed and irregular in the majority of patients of both the groups. The Actifit scaffold displayed a yellowish color that progressively disappeared during further evaluations after 40 months. The articular cartilage appeared intact without signs of progression of already existing articular injury in majority of the patients in both the groups.

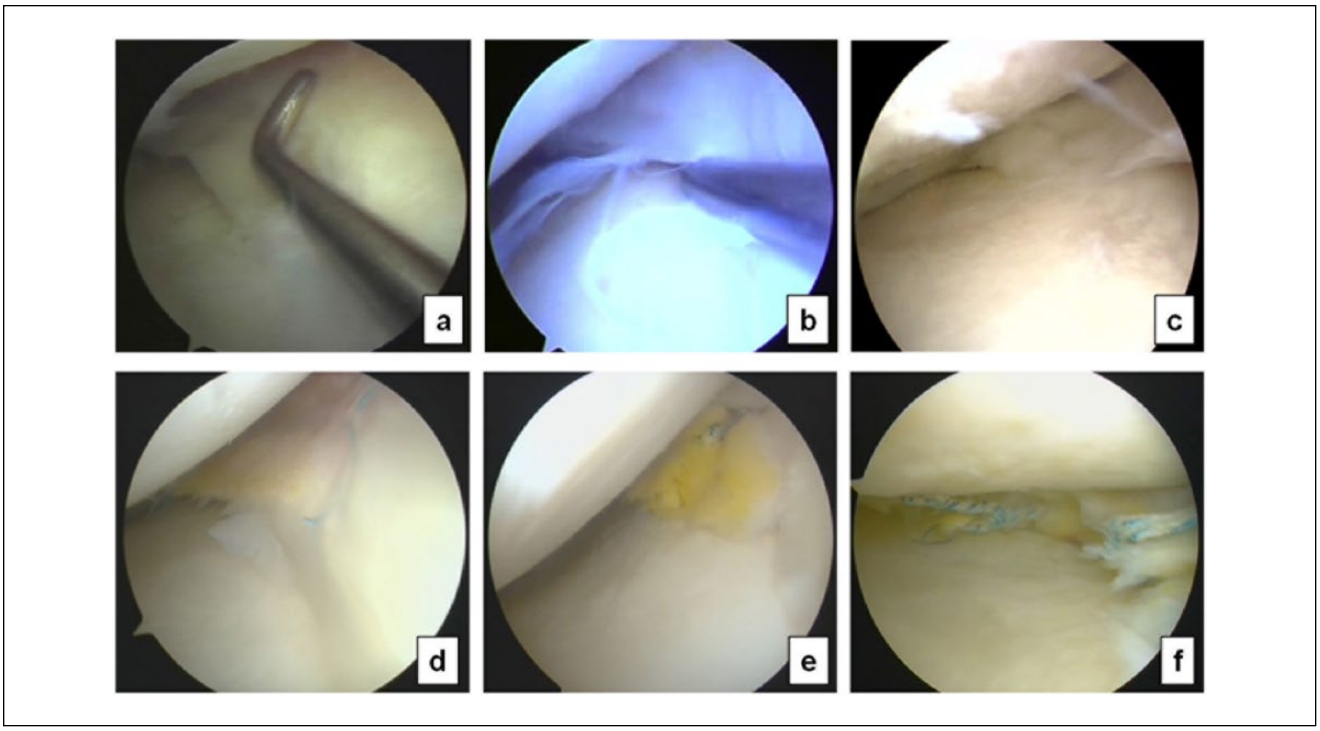

Figure 5. Second look arthroscopic evaluation: **a**, **b**, **c**—CMI at 7, 18, and 20 months, respectively; **c**, **d**, **e**—Actifit at 4, 18, and 27 months, respectively, after surgery showing intact, stable, and well-integrated scaffold.

Histological Evaluation

Histological analysis with light microscopy revealed that implant was present and was more compact filled with new tissue and extracellular matrix deposited in a heterogeneous way in both the groups. The biopsy samples from the CMI group showed more fibrous tissue that was rich in spindle and rounded fibroblast-like cells and blood vessels (**Fig. 6**). The Actifit biopsy samples appeared completely avascular with more cartilaginous-like appearance consisting plenty of chondroblast-like roundish, large, and active cells, and over time there was a greater percentage of smaller cells that had completely differentiated into chondrocytes, surrounded by a capsule and inserted in gaps, with few displaying a typical columnar arrangement (**Fig. 7**). All the biopsy samples showed vital cell and matrix structures with no evidence of necrosis. In 3 of the 11 Actifit patients who underwent second look arthroscopy, histological evaluation showed presence of plasma cells, macrophages, and rare lymphocytes, which could be a result of foreign body reaction; histological details of these patients are described in **Table 6**. However, we can consider this as grade 1, which is a low-grade foreign body reaction based on the classification suggested by Van Tienen *et al*.[24]

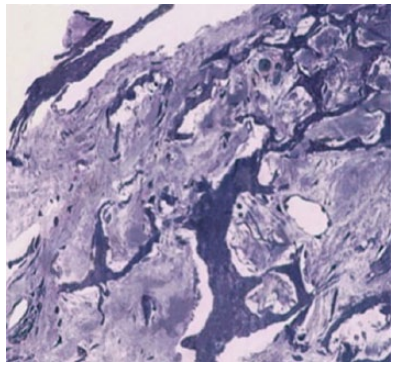

Figure 6. CMI histological evaluation at 7 months: Light microscopy of the implant stained with hematoxylin and eosin. The CMI scaffold is clearly evident. Connective tissue inside the lacunae and new vessels are evident. The new tissue appears fibrous, rich of spindle and round cell and with blood vessels present up to 2 years after implantation. Reguzzoni *et al.*[7]

Discussion

Our data showed clinical improvement in both groups of patients at 12 months after surgery and at final follow-up, which was statistically significant, and an intergroup statistical analysis showed no significant difference in improvement between the 2 groups. To our knowledge few studies compared the effectiveness of different scaffolds in treating irreparable partial medial meniscal lesions.

The patients treated with CMI were older than those in the Actifit group; however, these data are not significant (CMI: 38.7 ± 9.7; Actifit: 34.4 ± 11.4; $P = 0.1569$). Lysholm

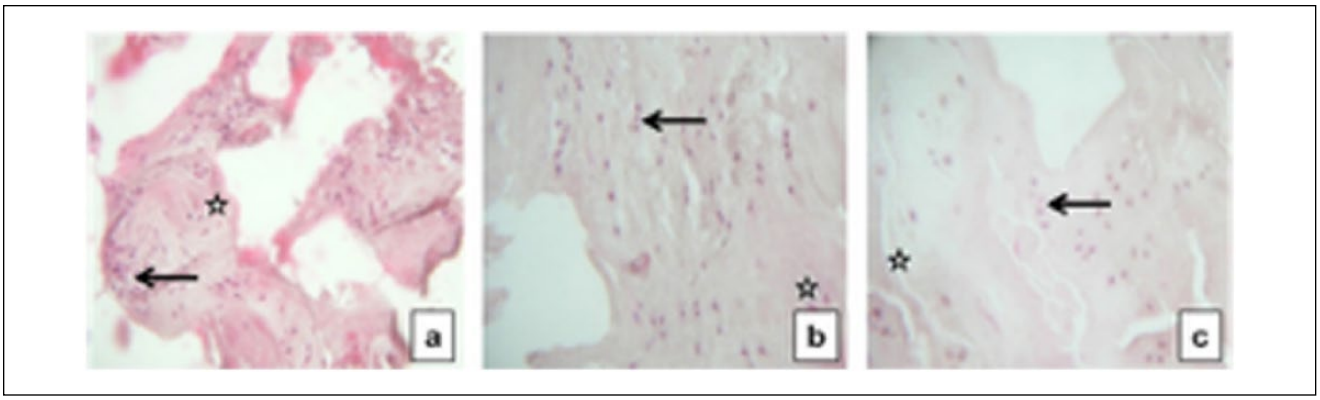

Figure 7. Actifit histological evaluation at 4, 18, and 27 months (**a**, **b**, and **c**) with hematoxylin and eosin stains: the implant is filled by new tissue cartilaginous like and avascular. Arrows indicating at new tissue regenerate; stars indicating at native meniscal tissue.

Table 6. Histological Findings After Second Look Arthroscopy and Concomitant Biopsy of the 2 Groups.

Sr. No.	Patient Initials	Group	a) Reason for Second Look Arthroscopy	Duration at Biopsy (months)	Histological Findings
1	AL	CMI	Chondrocyte implantation	7	b) Fibrous tissue, spindle and rounded fibroblast-like cells and blood vessels
2	DG	CMI	Debridement	3	c) Fibrous tissue, spindle and rounded fibroblast-like cells and blood vessels
3	GM	CMI	Microfracture	36	d) Fibrous tissue, spindle and rounded fibroblast-like cells and blood vessels
4	BA	CMI	Implant removal	12	e) Fibrous tissue, spindle and rounded fibroblast-like cells and blood vessels
5	TL	CMI	Chondrocyte implantation	8	f) Fibrous tissue, spindle and rounded fibroblast-like cells and blood vessels
6	GS	CMI	Persistent pain	6	g) Fibrous tissue, spindle and rounded fibroblast-like cells and blood vessels
7	IG	CMI	Implant removal	14	h) Fibrous tissue, spindle and rounded fibroblast-like cells and blood vessels
8	DF	Actifit	Joint stiffness	4	i) Avascular, cartilaginous-like appearance consisting plenty of chondroblast-like roundish, large, and active cells
9	GD	Actifit	Implant removal	11	j) Cartilaginous-like appearance consisting of plenty of chondroblast-like roundish, large, and active cells
10	BA	Actifit	Implant removal	18	k) Avascular, cartilaginous-like appearance consisting of plenty of chondroblast-like roundish, large, and active cells
11	DM	Actifit	Implant removal	22	l) Avascular, cartilaginous-like appearance consisting of plenty of chondroblast-like roundish, large, and active cells
12	ML	Actifit	Implant removal	27	m) Avascular, cartilaginous-like appearance consisting of plenty of chondroblast-like roundish, large, and active cells
13	CF	Actifit	Implant removal	34	n) Avascular, cartilaginous-like appearance consisting of plenty of chondroblast-like roundish, large, and active cells
14	DV	Actifit	Implant removal	41	o) Avascular, cartilaginous-like appearance consisting of plenty of chondroblast-like roundish, large, and active cells
15	CM	Actifit	Revision ACL reconstruction	45	p) Avascular, cartilaginous-like appearance consisting of plenty of chondroblast-like roundish, large, and active cells
16	MW	Actifit	Implant removal	14	q) Avascular, cartilaginous-like appearance consisting of plenty of chondroblast-like roundish, large, and active cells; with plasma cells, macrophages, and rare lymphocytes
17	GD	Actifit	Implant removal	15	r) Avascular, cartilaginous-like appearance consisting of plenty of chondroblast-like roundish; with plasma cells, macrophages, and rare lymphocytes large and active cells
18	CC	Actifit	Implant removal	20	s) Avascular, cartilaginous-like appearance consisting of plenty of chondroblast-like roundish, large, and active cells; with plasma cells, macrophages, and rare lymphocytes

scale has higher values in Actifit patients but it is not significant (CMI: 58.4 ± 17.3; Actifit: 67.0 ± 15.7; $P = 0.0775$). The higher Tegner baseline values in the Actifit group are the only ones statistically significant (CMI: 2ds 2-3; Actifit: 4ds 3-5) but they are completely random and may be related to the relatively younger patients compared with those treated with CMI. However, there are no difference in improvements between the scaffolds from preoperative to 6, 12, and 24 months after surgery (0.5918, 0.4916, 0.5918, respectively).

Spencer *et al*.,[21] in a similar study, presented similar results in a smaller number of patients with shorter follow-up; however, even in this study the type of scaffold did not influence the outcomes at final follow-up. Our final results confirmed similar clinical improvement at short- and mid-term

follow-up as described in previous studies.[11-14,17-22,25] Meniscal implantation along with concomitant procedure like ACL reconstruction has been reported to have less satisfactory results[26]; however, few other studies have reported that meniscal implantation along with a concomitant procedure does not affect the final clinical outcome.[11-13] In our study, we observed worse results when meniscal implantation was associated with a concomitant procedure. The preoperative status of articular cartilage also negatively influences the results of meniscal transplantation irrespective of the type of scaffold used, and it has also been proved in several previous studies that concluded that associated cartilage damage should not exceed ICRS grade 2 to obtain predictable results after meniscal implantation.[17,18,20,22] Similar to previous studies we have observed that a chronic knee injury pattern is accompanied by poor clinical and MRI results regardless of the type of scaffold implanted.[13,14] Two complications were seen in the CMI group, a case of neuroapraxia of the saphenous nerve, which can be attributed to its injury during a posteromedial incision made for inside-out sutures fixation, and a case of synovitis, which was related to poor patient compliance to our rehabilitation protocol. In the Actifit group, 4 cases of intra-articular effusion and pain were documented at different time points (26, 30, 36, and 42 months), which probably is related to implant reaction during the resorption process.

During MRI evaluation, morphology and signal intensity appeared different with both scaffolds when compared with normal meniscus. In fact, both products are porous structures and this justifies the hyperintense signal detected after implantation and even up to 2 years when the implant was still present with newly formed tissue still maturing. The signal intensity from the newly regenerated tissue seen within the scaffold gradually becomes hypointense over time, but the signal intensity never reduces to the level of a native menisci. Other studies showed similar results when these scaffolds beneficial effects were evaluated separat ely.[11-14,17-25] With regard to the signal intensity, we divided grade 2 of the Genovese classification into 2 subgroups, 2A and 2B, depending on the degree (greater or lesser) of signal hyperintensity. By doing this, considering the extreme subjectivity of the evaluation, we were able to differentiate the amount of hyperintensity among different patients that would have otherwise gone unnoticed. Moreover, this subdivision looks even more important while assessing the evolution of MRI signal with progression of time in the same subject. We did not find evidence of evolution of the degenerative processes at 2-year follow-up, and this could be related to a possible chondroprotective effect of these scaffolds; however, at the moment we are not aware of any clinical study focused on this possible effect.

During second look arthroscopy and concomitant biopsy, we found the Actifit scaffold to be of yellowish color, which could be due to the oxidation of polyurethane by the fatty acids of the joint environment. Histological evaluation of both scaffolds showed presence of new tissue without signs of cell death or necrosis. The biopsy from the CMI group showed more fibrous tissue rich in vessels, while Actifit showed more cartilaginous-like avascular tissue; in both cases the tissue was more compact with cells and extracellular matrix deposited in a heterogeneous way due to the compressive forces and due to varying distribution of the applied loads. Our findings are similar to that reported in the literature.[11,14,18,22] Regarding the Actifit histological appearance, Verdonk *et al*.[22] reported a trilaminar structure based on cells, extracellular matrix, and the blood vessels, which was not observed during our histological analysis. The authors also observed the presence of multiple fibrocartilaginous cells, which was also seen in our samples, but excluded presence of monocyte-macrophage cells and inflammatory reaction.[22] We also found 3 patients with intra-articular inflammatory cells, 2 of whom were completely asymptomatic, and only 1 presenting with significant effusion and pain during clinical evaluation. In our study, there are several limitations. First this is not a prospective randomized study; second is the extreme heterogeneity of the 2 groups with a greater number of chronic patients or those simultaneously treated with additional surgical procedures in the Actifit group. This important bias has to be seen positively since the Actifit scaffold was introduced later into clinical practice, after learning from the experience gained after years of use and related publications on the CMI scaffold. The best results in chronic patients were also taken into account and led to modifications in the indications of this procedure. Currently, the main indications for meniscal scaffold implantation are compartmental pain as a result of previous meniscectomy (chronic) and the irreparable meniscal tears (acute) just in case we assume the rapid evolution of degenerative disease (instability, misalignment that must be corrected). It has been emphasized by Kon *et al*.[19] that these scaffolds can also be used in complex knee lesions, where multiple comorbidities need to be properly addressed, and they have shown good clinical and MRI results at short-term evaluation.

Though we have presented only 2-year follow-up results and these patients have been treated at different time periods, there are only few studies in the literature comparing 2 different types of meniscal scaffolds treated in the same institution.

Conclusion

This study showed that both the meniscal implants are effective in improving the symptoms and joint function at short-term evaluation. MRI evaluation showed the presence of the scaffolds at 2 years, however with difference in shape, size, and intensity of the residual scaffold when compared with the native meniscus. We also noticed lack of progression of degenerative processes of the knee joint, suggesting a possible protective effect on articular cartilage.

Acknowledgments and Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The study has been approved by the Ethics Committee of the Ospedale di Circolo Fondazione Macchi, Varese, Italy (June 18,2013; Protocol Number 0023851; Registered Clinical Trials 54/2013).

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