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Scaffolds for partial meniscal replacement: an updated systematic review

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Introduction: Meniscectomy, a most common orthopaedic procedure, results in increased contact area of the articular surfaces of tibia and femur leading to early osteoarthritis. We systematically review the literature on clinical outcomes following partial meniscal replacement using different scaffolds.

Sources of data: We performed a comprehensive search of Medline, CINAHL, Embase and the Cochrane Central Registry of Controlled Trials. The reference lists of the selected articles were then examined by hand. Only studies focusing on investigation of clinical outcomes on patients undergoing a partial meniscal replacement using a scaffold were selected. We then evaluated the methodological quality of each article using the Coleman methodology score (CMS), a 10 criteria scoring list assessing the methodological quality of the selected studies (CMS).

Areas of agreement: Fifteen studies were included, all prospective studies, but only 2 were randomized controlled trials. Biological scaffolds were involved in 12 studies, 2 studies investigated synthetic scaffolds, whereas 1 remaining article presented data from the use of both classes of device. The mean modified CMS was 64.6.

Areas of controversy: Several demographic and biomechanical factors could influence the outcomes of this treatment modality.

Growing points: Partial replacement using both classes of scaffolds achieves significant and encouraging improved clinical results when compared with baseline values or with controls when present, without no adverse reaction related to the device.

Research: There is a need for more and better designed randomized trials, to confirm with a stronger level of evidence the promising preliminary results achieved by the current research.

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Introduction

The properties of the menisci in load distribution, shock absorption, force transmission, joint stability, lubrication and proprioception in the knee joint are well documented.[1–5] Meniscus tears are very common given the stresses imposed on the menisci because of this location and role within the knee, and meniscectomy is the most frequent orthopaedic surgical procedure undertaken: 1 million meniscectomies in the USA and over 400 000 in Europe are performed every year.[6] This procedure results in an increased contact area of the articular surfaces of the tibia and femur.[6] This could lead to early knee dysfunction and osteoarthritis, with associated knee pain, swelling and crepitus.[7–10]

Hence, it seems reasonable to preserve as much tissue as possible when performing a partial meniscectomy or a meniscal repair, to achieve better clinical outcomes than the total resection.[1,11] Meniscal allograft transplantation[12,13] and partial meniscus replacement prevent secondary osteoarthritis of the knee. The former is indicated when the patients underwent a total or subtotal resection.[6,14] Some studies have demonstrated low to moderate risk of disease transmission or immunological reaction associated with meniscal allograft implantation.[15–17]

Tissue engineering is attempting to produce scaffolds capable of fully supporting tissue neogenesis.[18] This has, therefore, led to the development of scaffolds to support the production of new fibrocartilage tissue comparable to meniscus in its intrinsic properties.[19] Two scaffolds are approved and available for clinical use: Menaflex® (ReGen Biologics Inc.), also known as collagen meniscal implant (CMI), is a biodegradable and biocompatible collagen type-I made from bovine tendinous tissue.[20] Actifit® (Orteq Bioengineering Ltd) is a synthetic polymeric scaffold made from aliphatic polyurethane. Both devices are designed for replacement of both lateral and medial meniscus.[20,21]

These devices represent a promising option for the treatment of meniscal injuries. We performed a systematic review to understand if partial meniscus replacement really improves clinical outcome in patients undergoing a meniscectomy, following a meniscal injury and whether this procedure is more beneficial than partial meniscectomy alone, if it can be suggested as a safe procedure and if there are differences in the final results achieved with the use of the two classes of devices. We evaluated the methodological quality of each study reviewed using the Coleman methodology score (CMS)[22] to assess the quality of available evidence in the published literature.

Materials and methods

Search strategy and study selection

A literature search was performed using combinations of keywords 'partial meniscus replacement', 'meniscal scaffold', 'collagen meniscus implant' and 'meniscus replacement using synthetic materials' with no limit regarding the year of publication. PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez/), Google Scholar (http://scholar.google.it/), CINAHL (http://www.ebscohost.com/cinahl/), Cochrane Central (http://www.thecochranelibrary.com/view/0/index.html) and Embase Biomedical (http://www.embase.com/) databases were accessed on the October 10, 2012 to search studies with no limits set during research. Given our language capabilities, we considered publications in Italian, Spanish, French and English.

At the first electronic search, 78 articles were identified. Two authors (R.P. and L.D.B.) independently reviewed the text of each abstract. Full-text versions were obtained to include or exclude the study. The reference lists of the selected articles were then reviewed carefully to identify articles not identified at the electronic search. All journals were considered, and all relevant articles were retrieved. Studies focusing on clinical outcomes of patients following a partial meniscal replacement were selected. Biomechanical reports, studies on animals or cadavers, exclusive *in vitro* analysis, case reports, literature reviews, technical notes, letters to editors, instructional course and studies focusing only on complications were excluded. Twenty-four articles investigating the clinical outcomes following partial meniscal repair using a biodegradable scaffold were identified. To avoid bias, all these articles were reviewed and discussed by all the authors: seven articles were excluded because they did not report clinical data. Finally, 15 publications relevant to the topic were included (Figure 1).

Quality assessment

Two investigators (R.P. and L.D.B.) separately evaluated each article using the CMS, a 10 criteria validated scoring system assessing the study methodological quality, with final score ranging from 0 to 100. An investigation scoring 100 would represent a perfect study design with no influence of chance, biases and confounding factors. The two investigators discussed scores, where more than a two point difference was evident, until consensus was reached. Additionally, data on gender, age, type of surgery, comorbidities and complications were recorded as well.

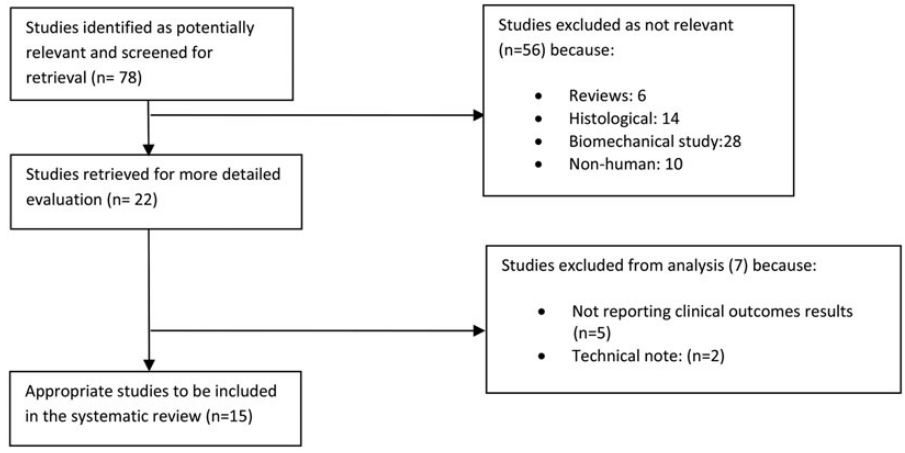

Fig. 1 Process of inclusion of the studies.

Results

Number and type of studies

Fifteen studies, all prospective, were included in the present review, all focusing on clinical outcomes of patients who underwent partial meniscal replacement with a scaffold after a subtotal meniscectomy. There were 2 randomized controlled trials,[20,23] 1 was a prospective cohort study[24] and 12 were case series.[25–36] Studies reviewed were published between 1997 and 2012.

Pre-operative features

The mean age at surgery was 36.9 years, ranging from 16[24,36] to 67.[24]

Study size and follow-up

A total of 624 patients were treated, 439 males and 108 females reported. As for the remaining patients, sex was unstated in three studies.[20,28,34] Mean follow-up for the included studies was 56 months. Details on demographic data of each study are available in Table 1.

Methodology score

The average modified CMS was 64.6 (range from 37[28] to 83[23]). The total CMSs and the details for each criterion of this evaluation are given in Table 2.

Table 1 Demographic data.

Study	Level of evidence	No. of patient recruited	Men	Women	Mean follow-up (months)	Mean age at surgery
		Total = 624	Total = 439	Total = 108		
		Average = 41.6	Average = 36.6	Average = 9	Average = 52.2	Average = 37
		SD = 75.86	SD = 65.8	SD = 19	SD = 40.3	SD = 4.7
Rodkey *et al.*[29]	4	8	8	0	28	40
Rodkey *et al.*[23]	1	311	243	68	59	39.3
Stone *et al.*[32]	4	10	8	2	36	39.3
Steadman and Rodkey[31]	4	8	8	0	69,6	40.0
Reguzzoni *et al.*[28]	4	4	Nr	Nr	6	38.0
Linke *et al.*[20]	1	39	Nr	Nr	24	41.7
Zaffagnini *et al.*[35]	4	8	8	0	81.6	31.0
Zaffagnini *et al.*[34]	4	34	Nr	Nr	58.6	41.5
Zaffagnini *et al.*[24]	2	33	33	0	133	40.0
Zaffagnini *et al.*[36]	4	24	20	4	26	36.3
Bulgheroni *et al.*[25]	4	34	25	9	68	39.0
Monllau *et al.*[27]	4	25	20	5	135,6	29.2
Efe *et al.*[26]	4	10	8	2	12	29.0
Verdonk *et al.*[33]	4	52	39	13	24	30.8
Spencer *et al.*[30]	4	24	19	5	21	35.0

Nr, not reported.

Subject selection

Subject selection criteria were satisfactorily described in 10 studies (66.6%),[23,24,26,27,29–33,36] and reliable and sensitive validated scoring systems were used in 11 studies (73.3%).[23–27,29,31,33–36] With regard to the 'outcome assessment' section of the CMS, adequate scores were reported in six articles (40%).[23,24,26,27,30,31,36]

Surgical description and post-operative rehabilitation

Concerning the description of the surgical technique, the maximum rating score of 5 points was assigned to eight articles (53.3%),[20,24,26,27,29–31,35] whereas at least 3 points were obtained by six studies (40%).[23,25,32–34,36] Only one study scored 0 for this criterion because the surgical procedure was barely stated.[28] Post-operative rehabilitation was well described in six studies (40%).[20,23–26,29] The exercise protocol was not even stated by one study.[28]

Type of implant used

Twelve of the total 15 studies (80%)[20,23–25,27–29,31,32,34–36] assessed the clinical outcomes of patients treated using a CMI. Two studies[26,33]

Table 2 Coleman methodology scores.

Study	Size of the study	Mean follow-up	Number of different surgical procedures	Type of study	Diagnostic certainty	Description of surgical procedure	Description of post-operative rehabilitation	Outcome criteria	Procedure for outcome	Description of subject selection process	Coleman score
Rodkey *et al.*[29]	0	5	10	10	5	5	10	8	7	8	68
Rodkey *et al.*[23]	10	5	0	15	5	3	10	8	12	15	83
Stone *et al.*[32]	0	5	10	0	5	3	5	5	7	8	48
Steadman and Rodkey[31]	0	5	10	0	5	5	5	10	10	8	58
Reguzzoni *et al.*[28]	0	0	10	0	5	0	0	3	4	5	27
Linke *et al.*[20]	4	2	0	15	5	5	10	4	8	5	58
Zaffagnini *et al.*[35]	0	5	10	0	5	5	5	8	7	5	50
Zaffagnini *et al.*[34]	4	5	10	0	5	3	5	8	7	0	47
Zaffagnini *et al.*[24]	4	5	0	10	5	5	10	10	11	8	68
Zaffagnini *et al.*[36]	4	5	10	10	5	3	5	8	11	8	69
Monllau *et al.*[27]	4	5	10	0	5	5	5	8	10	10	62
Bulgheroni *et al.*[25]	4	5	10	0	5	3	10	8	6	5	56
Efe *et al.*[26]	0	2	10	0	5	5	10	8	12	8	60
Verdonk *et al.*[33]	7	2	10	0	5	3	5	8	8	8	56
Spencer *et al.*[30]	4	5	10	0	5	5	5	5	10	10	59

assessed patients treated with the Actifit® synthetic scaffold, whereas Spencer *et al.*[30] compared the outcomes of patients treated either with Menaflex® collagen meniscus implant (ReGen Biologics, USA) or Actifit® (Orteq Bioengineering Ltd) (Table 3).

Reported failures and complications

A rate of 10.25% of patients reported a failure, whereas 5.25% of patients underwent a severe complication related or possibly related to the scaffold.

A complete overview of the rate of implant failures and complications occurred is given in Table 4.

Outcome measures

Common and validated clinical and functional outcome scoring systems were used to report results obtained in the studies included in this review (Fig. 2). The most commonly used rating scales were Lysholm score,[20,23–25,27–31,33,34,36] Tegner index[23–25,28–31,34,36] and IKDC.[20,24,30,33,35,36]

Outcome data

Thirteen of the 15 studies[20,23–25,27–32,34–36] included in this review reported the results achieved by partial meniscus repair using a CMI, whereas 3 studies[26,30,33] reported on the use of Actifit® (Orteq Bioengineering Ltd) polyurethane scaffold (Table 3).

Table 3 Implant used.

Study	Class of implant	Type of implant
Rodkey *et al.*[29]	Biological	Self-produced CMI
Rodkey *et al.*[23]	Biological	Menaflex® (ReGen Biologics Inc.)
Stone *et al.*[32]	Biological	Self-produced CMI
Steadman and Rodkey[31]	Biological	Menaflex® (ReGen Biologics Inc.)
Reguzzoni *et al.*[28]	Biological	Menaflex® (ReGen Biologics Inc.)
Linke *et al.*[20]	Biological	Menaflex® (ReGen Biologics Inc.)
Zaffagnini *et al.*[35]	Biological	Menaflex® (ReGen Biologics Inc.)
Zaffagnini *et al.*[34]	Biological	Menaflex® (ReGen Biologics Inc.)
Zaffagnini *et al.*[24]	Biological	Menaflex® (ReGen Biologics Inc.)
Zaffagnini *et al.*[36]	Biological	Menaflex® (ReGen Biologics Inc.)
Bulgheroni *et al.*[25]	Biological	Menaflex® (ReGen Biologics Inc.)
Monllau *et al.*[27]	Biological	Menaflex® (ReGen Biologics Inc.)
Efe *et al.*[26]	Synthetic	Actifit® (Orteq Bioengineering Ltd)
Verdonk *et al.*[33]	Synthetic	Actifit® (Orteq Bioengineering Ltd)
Spencer *et al.*[30]	Biological	Menaflex® (ReGen Biologics Inc.) and
	Synthetic	Actifit® (Orteq Bioengineering Ltd)

Table 4 Failure and complication rates and details.

Study	Failure/reoperations	Complications rate and details
Rodkey *et al*.[29]	Implant group 12.5% (1 out of 8): excessive scar formation	Not related to the scaffold
Rodkey *et al*.[23]	Implant group 9.5% (13 out of 160): 7× persistent pain, 3× swelling/effusion, 1× stiffness, 1× locking and 2× instability	Implant group: 7.5% (12/157): 7 out of 12 were possibly related to the collagen meniscus implant, 2× pain, 4× swelling, 1× instabilty, 1× nerve injury, 1× infection, 1× DVT, 1× wound related and 1× patellofemoral symptoms.
	Control group 22.7% (20 out of 151): 15× persistent pain, 1× swelling, 3 locking and 2 instability	Control group: 7.3% (11 out of 151): 7× pain, 1× swelling, 0× instability, 1× nerve injury, 1× infection and 1× DVT.
Linke *et al*.[20]	Implant group: 2.5% (1 out of 9): disorganization of the implant and luxation	Not reported
Zaffagnini *et al*.[24]	Implant group 11.1% (2 out of 18): 1× pain and swelling, 1× swelling Control group 11.1% (2 out of 18): 1× pain and swelling, 1× swelling	Not reported
Zaffagnini *et al*.[36]	Implant group 4.16% (1 out of 24): persistent pain and knee swelling	Not related to the scaffold
Bulgheroni *et al*.[25]	Implant group 7.14% (2 out of 28): 2× HTO (implant had to be removed).	Implant group 7.14% (2 out of 28): 1× paraesthesia of the leg, 1× continuous swelling
Monllau *et al*.[27]	Implant group 8% (2 out of 25): failure defined as infection caused by the implant or mechanical failure of the implant	Implant group 31.8 % (7 out of 22): knee swelling
Verdonk *et al*.[33]	Implant group 17.3 % (9 out of 52): 3× pain, 2× non-integrated scaffold, 1× tear in tissue/scaffold, 1× infection, 1× eventual UKA and 1× dislocation of tissue/scaffold	Not reported
Spencer *et al*.[30]	Menaflex group: 4.16% (1 out of 24): acute pain, treated with debridement and implantation of ActifIT Actifit group: no complications	Not related to the scaffold
Zaffagnini *et al*.[34]	No failures	Not related to the scaffold
Efe *et al*.[26]	No Failures	Not related to the scaffold
Stone *et al*.[32]	Not reported	Not reported
Steadman and Rodkey[31]	Not reported	Not reported
Reguzzoni *et al*.[28]	Not reported	Not reported
Zaffagnini *et al*.[35]	Not reported	Not related to the scaffold

DVT, deep vein thrombosis; HTO, high tibial osteotomy; UKA, unicompartmental knee arthroplasty.

Biological implant outcome data

Stone *et al*.[32] investigated the outcome of the CMI in 10 subjects diagnosed with an irreparable tear of the meniscal cartilage or a major loss

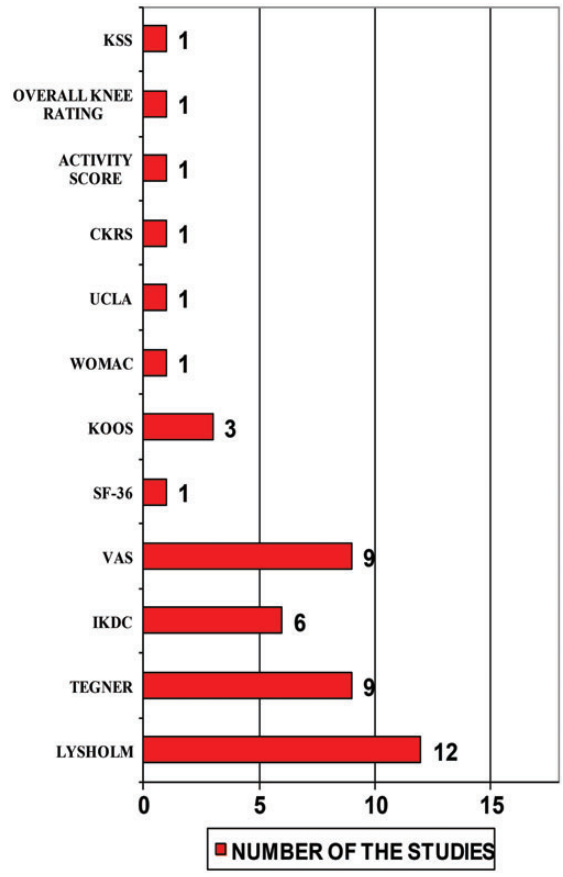

Fig. 2 Scores used to assess the outcomes.

of meniscal cartilage. They reported MRI findings indicating ongoing ingrowth and regeneration of tissue. The gross appearance of the regenerated tissue at 6 months was similar to the fibrous composition of meniscal cartilage. After 36 months from the procedure, all patients reported a decrease in symptoms. None of the patients showed signs of immune response.

Rodkey *et al.*[29] started investigating their self-developed collagen biological scaffold in 1999 on a small cohort of eight patients. Their clinical, radiological and histological preliminary findings were encouraging, with all patients regaining an activity level, showing signs of fibrocartilage ingrowth over the device and inhibition of the osteoarthritic changes of the joint over 24 months. This initial study led to a more recent multicentre randomized controlled trial,[23] where they used CMI to treat over 300 patients divided into 2 groups: 1 group who had no prior meniscal surgery on the site (acute) and the second group that had already been treated surgically in the past for a meniscal injury

(chronic). They evaluated clinical outcomes and macroscopic and microscopic appearance of the scaffold with a mandatory second-look arthroscopy and biopsy on the site for all subjects who received the implant. During their long-term follow-up over 7 years, they noted how patients who already had prior surgery on the site and received the implant had significantly improved outcomes when compared with controls undergoing just a meniscectomy, whereas the 'acute group', consisting of patients treated surgically for the first time, did not score higher outcomes values than a group of patients treated with partial meniscectomy as measured by Lysholm score, Tegner, VAS and a self-rating questionnaire. No effect on the chondral regeneration process was found at imaging assessment. There was evidence of meniscus-like tissue colonizing the scaffold in all patients evaluated 1 year after the procedure, with over 75% of the scaffold being reabsorbed. Reoperation and complication rate was also very low, and comparable to isolated meniscectomy.

Steadman and Rodkey[31] found improved outcomes for eight patients at a mean 5.8 years of follow-up after partial meniscal reconstruction with scaffold. Mean Lysholm and Tegner activity scores were relevantly improved at the latest evaluation. Magnetic resonance imaging demonstrated no degeneration in the chondral surfaces and progressive maturity of the implant. At second look arthroscopy, the authors reported 69% filling of the device with regenerative tissue.

Bulgheroni *et al*.[25] presented the results of 28 patients at 5 years of follow-up after they received Menaflex® replacement for a symptomatic deficiency of medial meniscal tissue. Clinical results were good to excellent at final follow-up, and Lysholm and Tegner scores showed significant short-term improvement and were unchanged between 2 and 5 years post-operatively. Radiographic imaging showed that the osteoarthritic process did not evolve after the implantation of the device, whereas the signal intensity of this at MRI gradually decreased through time, proving an ongoing evolution of the implant.

Linke *et al*.[20] treated selected patients with a genu varus and a subtotal loss of the medial meniscus performing a partial replacement with CMI associated with a corrective high tibial osteotomy. Controls received only the high tibial osteotomy. The recorded Lysholm score, IKDC score and subjective pain data 24 months post-operatively showed only slight and non-significant differences when compared with the control group.

Zaffagnini *et al*. published a long-term follow-up of patients' meniscus partial replacement using Menaflex®. In an initial study in 2007,[35] they presented clinical outcome and reported on the safety of the procedure on eight patients after 8 years of follow-up. No adverse reaction was reported, and for all patients, both the subjective CKRS score and

the objective IKDC score showed improvement in all patients except one. Two years later,[34] they analysed 30 patients undergoing partial replacement of the medial meniscus and 12 patients with procedures on the lateral meniscus. Post-operatively stability was normal in all cases. A normal range of motion was observed in 83% (25 out of 30) of patients treated for their medial meniscus, whereas in all patients who underwent lateral meniscal implant, the range of motion was normal. All clinical scores considered showed a significant improvement, particularly with regard to pain relief measured with the VAS scale for all patients. The same authors,[24] in another publication work only on medial meniscus partial replacement, confirmed their previous conclusion on 33 patients randomized to prospectively evaluate the results of the implantation, showing higher clinical outcomes as measured by IKDC and CKRS scores when compared with controls treated with partial meniscectomy at a minimum 6 years of follow-up. No complication was recorded. The radiographs of only two patients showed a slight increase in arthritis, whereas the other patients had no evolution either negatively or positively. MRI showed mixoid degeneration signal at the implant site in five cases. Finally, their most recent report[36] focused on procedures on the lateral meniscus, reporting the same efficacy found for the medial CMI, relevant improvement in all subjective and clinical scores measured, with decreased pain and improved knee function in over 90% of patients treated at 2 years of follow-up. MRI assessment also showed the typical decrease in size of the implant over time already found in their previous trials.

Monllau *et al.*[27] evaluated the clinical outcome of 25 patients who received a CMI implant in the injured medial meniscus after a mean follow-up of 135 months. A statistically significant improvement was observed in Lysholm score and VAS scale ($P < 0.001$). The results were good or excellent in 83% of the population. The most common finding on MRI was an implant that had reduced in size with partial integration into the host meniscus, and with an unrecognizable interface between the residual meniscus and the scaffold.

Reguzzoni *et al.*[28] studied the clinical outcomes and the histological findings of four patients after meniscal reconstruction with CMI. The Lysholm score and Tegner activity scale improved in all patients at 6 months post-operative evaluation. They also confirm the evidence, as seen with different microscopy methods, of tissue ingrowth supporting that CMI possesses tissue-conductive properties for regeneration of meniscus-like tissue.

Synthetic implant outcome data

Efe *et al.*[26] in a prospective study used the synthetic Actifit® scaffold to treat 10 symptomatic patients after medial partial meniscectomy. All

patients reported improved outcomes when compared with baseline. At 12 months of follow-up, the MRI imaging showed overall stability of the implants, and none of them reabsorbed in such a short time. A statistically significant increase in all subdomains of the KOOS and KSS outcome score was recorded ($P < 0.05$), whereas improvements in UCLA activity scale and VAS did not reach significance. No complications or adverse reactions were reported for any of the cases.

Verdonk *et al*.[33] designed a multicentre 1 year of follow-up study consisting of 52 patients treated with Actifit® for the treatment of painful irreparable partial meniscal defects. Clinically and statistically significant improvements ($P < 0.0001$) when compared with baseline were reported in all clinical outcome scores at 24 months (VAS, IKDC, KOOS and Lysholm). The reported rate of failure was about 20%; therefore, nine patients required reoperation with a significantly higher occurrence on the lateral compartment.

Spencer *et al*.[30] compared the clinical and imaging outcomes of patients treated with CMI implant and those treated with Actifit® to evaluate whether a substantial difference in post-operative results was noted. Both medial and lateral menisci conditions were treated. No substantial differences from the two groups were found. Almost all patients (21 out of 23) had significantly improved Lysholm score, KOOS score, Tegner activity score and IKDC score at last follow-up (18 months for Actifit® and 24 months for CMI). Imaging assessment showed a variable amount of regenerative tissue infill of the scaffold for all patients treated.

A detailed report of all clinical outcome data is given in Table 5, whereas an overview of the imaging and histological findings is given in Table 6 and Table 7.

Discussion

Meniscectomy is the most common orthopaedic surgery performed in the USA and Europe. To avoid the irreversible joint damage known to be caused by this procedure in the long-term, preventing joint stability, it is reasonable to consider a meniscal replacement of the resected tissue.[7,37,38]

Several studies have investigated the results achieved using the CMI because it was first developed, described and used by Stone, Steadman, Rodkey and Li during the 1990s.[29,39] They developed this collagen matrix scaffold to support the ingrowth and regeneration of new meniscus-like tissue following a partial meniscectomy. The shape is similar to the human meniscus, and the scaffold is extensively

Table 5 Clinical outcome data

Study and year	Score	Mean pre-operative	Mean post-operative (last follow-up)
Rodkey *et al.*[29]	Lysholm	Implant group = 75.2	Implant group = 93.4
	Tegner	Implant group = 3.1	Implant group = 5.25
	VAS	Implant group = 23	Implant group = 1.75
Rodkey *et al.*[23]	Lysholm functional score	Implant group Acute: 26 Chronic: 16 Control group Acute: 28 Chronic: 22	Implant group Acute: 90 Chronic: 79 Control group: Acute: 87 Chronic: 78
	Pain score (1–100)	Implant group Acute: 16 Chronic: 18 Control group Acute: 21 Chronic: 18	Implant group Acute: 5 Chronic: 19 Control group Acute: 6 Chronic: 21
	Tegner activity index	–	Implant group Acute: 41% activity regained Chronic: 42% activity regained Control group Acute: 41% activity regained Chronic: 29% activity regained(Absolute numbers not reported)
Stone *et al.*[32]	Activity score	Implant group = 1.5	Implant group = 2.2
	Overall knee rating	Nr	Implant group 2.0 at 24 months of follow-up 1.4 at 26 months of follow-up
Steadman and Rodkey[31]	Lysholm	Implant group = 75	Implant group = 88
	Tegner	Implant group = 7.4	Implant group = 6.0
	VAS	Implant group = 23	Implant group = 11
Reguzzoni *et al.*[28]	Lysholm	Implant group = 62.25	Implant group = 93.75
	Tegner	Implant group = 2.3	Implant group = 4.5
Linke *et al.*[20]	Lysholm functional score	Implant group = 65.2 Control group = 93.6	Implant group = 67 Control group = 91
	IKDC	Implant group = 60 Control group = 53	Implant group = 83 Control group = 77
	VAS	Implant group = 4.9 Control group = 2.2	Implant group = 5.2 Control group = 1.5
Zaffagnini *et al.*[35]	CKRS	Implant group = 240	Implant group = 391.25
	IKDC	Implant group = 5C, 3B	Implant group = 5A,3B
Zaffagnini *et al.*[34]	Lysholm	Lateral = 68.2 Medial = nr	Lateral = 95.2 Medial = 95.0

Continued

Table 5 *Continued*

Study and year	Score	Mean pre-operative	Mean post-operative (last follow-up)
	Tegner	Lateral = 3.2 Medial = 4.3	Lateral = 6.0 Medial = 5.4
	VAS	Lateral = 8.8 Medial = 5.0	Lateral = 2.3 Medial = 1.0
	WOMAC	Lateral = nr Medial = nr	Lateral = nr Medial = 96.4
Zaffagnini *et al*.[24]	Lysholm functional score	–	Implant group = 90 Control group = 80
	Tegner activity scale	–	Implant group = 75 Control group = 50
	VAS	–	Implant group = 1.2 Control group = 3.3
	IKDC	–	Implant group = 7A, 10B Control group = 4B, 12C
	SF-36 Physical Health Index	–	Implant group = 53.9 Control group = 44.1
	SF-36 Mental Health Index	–	Implant group = 54.7 Control group = 43.8
Zaffagnini *et al*.[36]	Lysholm	Implant group = 64.0	Implant group = 92.7
	VAS	Implant group = 55.2	Implant group = 19.5
	Tegner	Implant group = 3	Implant group = 5
	IKDC	Implant group = 6A,14B,4C,0D	Implant group = 20A,3B,0C,1D
Bulgheroni *et al*.[25]	Tegner	Implant group = 3.7	Implant group = 5.2
	Lysholm	Implant group = 58	Implant group = 94
Monllau *et al*.[27]	Lysholm	Implant group = 59.9	Implant group = 87.56
	VAS	Implant group = 5.5	Implant group = 2
Efe *et al*.[26]	KSS	Implant group Knee score = 61.8 Function score = 60	Implant group Knee score = 87.1 Function score = 90.5
	KOOS	Implant group Symptoms = 60.8 Pain = 45.7 Adl = 53.7 Sports = 29.5 QoL = 27.6	Implant group Symptoms = 85.9 Pain = 82.5 Adl = 90 Sports = 79 QoL = 70.8
	VAS	Implant group = 4.2	Implant group = 2.05
	UCLA	Implant group = 5	Implant group = 6.4
Verdonk *et al*.[33]	VAS	Implant group = 45.7	Implant group = 20.3
	IKDC	Implant group = 45.4	Implant group = 70.1
	Lysholm	Implant group = 60.1	Implant group = 80.7
	KOOS	Implant group Symptoms = 64.6 Pain = 57.2 Adl = 68.8 Sports = 30.5 QoL = 33.9	Implant group Symptoms = 78.3 Pain = 78.6 Adl = 84.2 Sports = 59.0 QoL = 56.6
Spencer *et al*.[30]	Lysholm	Collagen implant = 62 Polyurethane scaffold = 56	Collagen implant = 83 Polyurethane scaffold = 87

Continued

Table 5 *Continued*

Study and year	Score	Mean pre-operative	Mean post-operative (last follow-up)
	Tegner	Collagen implant = 3.7 Polyurethane scaffold = 3.8	Collagen implant = 5.2 Polyurethane scaffold = 4.4
	IKDC	Collagen implant = 48 Polyurethane scaffold = 42	Collagen implant = 72 Polyurethane scaffold = 74
	KOOS	Collagen implant Pain = 60.3 Symptoms = 54.1 Adl = 69.3 Sports = 35 QoL = 31.5 Polyurethane scaffold Pain = 56.7 Symptoms = 52.5 Adl = 66.8 Sports = 37.3 QoL = 27.8	Collagen implant Pain = 88.8 Symptoms = 79.7 Adl = 94 Sports = 62.2 QoL = 57 Polyurethane scaffold Pain = 85.6 Symptoms = 87.6 Adl = 93 Sports = 66 QoL = 61.4

ADL, activity daily living; Nr, not reported; QoL, quality of life.

reabsorbed in 12–18 months, as demonstrated by the altered signal at MRI and the histological findings after biopsy in numerous studies.[25,27,28]

The clinical use of a synthetic device as an alternative to CMI in reconstructing irreparable partial tear of the meniscus has been documented only in the last decade. Actifit® (Orteq Limited, London, UK) is a highly porous device made from aliphatic polyurethane, characterized by 80% polycaprolactone. This device as well works like a shape, where cells can migrate and proliferate to a meniscus-like tissue.[40] Gradual integration into the meniscal tissue repaired occurs gradually in 5 years being degraded by hydrolysis into non-toxic components.[30] Menaflex® (ReGen Biologics, USA) and Actifit® (Orteq, UK), even if they have totally different compositions, have a comparable surgical implantation technique to the above.[41,42] After preparation of the remnant, the implant is manipulated into place. The vascularized zone of the menisci (red–red or red–white zone) should be reached, leaving the rime bleeding to allow tissue ingrowth and cell colonization inside and over the scaffold.[43] Fixation can be achieved using a combination of different methods depending on the operator's preference and experience.[25] In-to-out or all inside suture systems were adopted in the trials reviewed with good results for both of them. This last approach is relatively recent and is useful to avoid the posterior incision and related complications.[34] No author focused on the possible differences in final results achieved using the two techniques.

Table 6 Radiological findings.

Study	Modality	Findings at last follow-up
Rodkey *et al*.[29]	MRI	The comparison of the serial MRI through 1 year of follow-up showed a decreasing signal intensity with time suggesting an ongoing maturation process of the newly regenerated tissue
Bulgheroni *et al*.[25]	MRI	The meniscal implant appeared not to be completely resorbed Often, there was a size reduction, but it remained stable over time.
Steadman and Rodkey[31]	X-ray	At 5.8 years of follow-up, there is evidence of conserved medial surfaces
	MRI	Between 2 and 5.8 months of follow-up, MRI images show a gradual progressive integration of the scaffold with a lower signal similar to native fibrocartilage at last follow-up
Stone *et al*.[32]	X-ray	36 months after the implantation, radiography showed no differences with the regard to the joint space when compared with pre-operative findings
	MRI	Progressive ongoing ingrowth and regeneration of tissue with a less distinctive interface between the native meniscal rim and the implant
Monllau *et al*.[27]	MRI	The implant had reduced in size, with a slightly hyperintense signal, with partial integration into the native meniscus and with an unrecognizable interface between the residual and synthetic meniscus
Spencer *et al*.[30]	MRI	Mixed appearance of the tissue/scaffold construct was observed varying from good structural integrity (infill) to marked erosion
Efe *et al*.[26]	MRI	Stable appearance of the scaffold and host tissue at 6 and 12 months of follow-up. A significant hyperintensity is present in all scaffold indicating an incomplete reabsorption. No evidence of inflammation
Zaffagnini *et al*.[35]	X-ray	6 out of 8 (75%) patients showed preserved articular surface and joint space with no medial degeneration
	MRI	Mixoid degeneration signal at the implant site in 5 out of 8 (62.5%) cases. The appearance of the new tissue showed a continuous maturation in 4 out of 8 (50%) cases, whereas in 3 out of 8 (37.5%) cases, the MRI images remain similar at 2 year control, and in 1 out of 8 (12.5%), the implant disappeared
Zaffagnini *et al*.[34]	MRI	At 10 years of follow-up, the medial implant has a good signal and the cartilage is preserved
Zaffagnini *et al*.[24]	MRI	Evaluation in the implant group showed: 11× myxoid degeneration signal, 4× normal signal with reduced size and 2× no recognizable implant
Zaffagnini *et al*.[36]	MRI	Evaluation of size and shape showed a small implant with a regular and/or irregular shape in 18 out of 24 cases (75.0%). Regarding the MRI signal intensity, most of patients showed a mild hyperintense signal 50% (12 out of 24)
Reguzzoni *et al*.[28]		Not reported
Rodkey *et al*.[23]		Not reported
Linke *et al*.[20]		Not reported
Verdonk *et al*.[33]		Not reported

The goal of our study was to assess, by reviewing the current literature available on these implants, whether the outcome reported on patients undergoing partial replacements makes this procedure safe and effective in patients and irreparable partial meniscal tear.

Regarding effectiveness, of the 15 studies included in our investigation, all but 2 concluded that the replacement procedure achieved

Table 7 Histological findings.

Study	Findings at time of biopsy
Rodkey *et al*.[29]	At 12 months of follow-up, histological examination showed the new tissue with a stable interface with the native meniscus rim, and there was evidence of invasion of fibrochondrocytes-like cells and new tissue regeneration. No inflammatory cells were present
Rodkey *et al*.[23]	The implant appears to provide a scaffold for the formation of meniscus-like fibrochondrocytic matrix by the host. In all patients, the meniscus implant was demonstrated, providing a variable absorption into the new fibrochondrocytic matrix. In $<5\%$ of the cases, inflammation of the synovium in the biopsy specimen was observed
Bulgheroni *et al*.[25]	At 5 years of follow-up, histological analysis revealed two different connective tissues, one more compact and the other looser with presence of fibroblast-like cells and vessels. No phagocytes or macrophages were observed
Reguzzoni *et al*.[28]	Light microscopy: at 6 months of follow-up, the histological specimen shows a tissue invasion disrupting the multilamellar structure characterizing the collagen scaffold. The filling tissue shows the characteristic of a connective tissue with fibroblast-like cells, surrounded by newly formed extracellular matrix and vessels. No phagocytes or macrophages were present Scanning electron microscopy: the structure of the scaffold at 6 months of follow-up is less evident than pre-operative time. The biopsy samples show a compressed upper and lower lamellae with cristae that have the purpose to provide a mechanical strength Transmission electron microscopy: evidence of pseudopodia in the new synthesized collagen fibrils showing an important tendency to organize in bundles
Steadman and Rodkey[31]	Biopsy examination of the new tissue showed the presence of fibrocartilage. The cells had the appearance of normal meniscus fibrochondrocytes, and no inflammatory infiltrates were observed
Stone *et al*.[32]	The collagen implant was progressively invaded and replaced by new collagen and cells typical of meniscal fibrochondrocytes. No inflammatory cells or signs of immunological reaction were noted. The three-month biopsy specimens revealed a substantial amount of remaining collagen implant
Linke *et al*.[20]	Not reported
Verdonk *et al*.[33]	Not reported
Monllau *et al*.[27]	Not reported
Spencer *et al*.[30]	Not reported
Efe *et al*.[26]	Not reported
Zaffagnini *et al*.[35]	Not reported
Zaffagnini *et al*.[34]	Not reported
Zaffagnini *et al*.[24]	Not reported
Zaffagnini *et al*.[36]	Not reported

significant and encouraging improved clinical results when compared with baseline values or with controls when present. Rodkey *et al*.[23] found that patients with an acute meniscal injury with subtotal loss of tissue treated with CMI implant had no different final outcomes when compared with controls who underwent a simple partial meniscectomy. Linke *et al*.[20] as well showed a worrying rate of unsatisfactory clinical results: 8 of 23 patients showed poor clinical results and only 8 patients showed a complete healing of the implanted scaffold at second-look arthroscopy. However, this last work focused on procedures performed

on a selected cohort of patients and a concomitant varus knee and designed the study to see whether a corrective osteotomy alone was as effective as the osteotomy associated with partial meniscus replacement. They then concluded that the difference in outcomes between these two management options is not significant, and, therefore, they do not support the association of high tibial osteotomy (HTO) with meniscal replacement. Nevertheless, this study is the only one precisely investigating the influence of malalignment on the expected results of meniscal replacement, and the outcomes obtained indicate how this factor could influence decision making of meniscal injuries. This supposed lack of interest for research on associated malalignment condition may be justified by the inclusion criteria of the studies that always excluded patients with a knee varus or valgus malalignment. A better comprehension of this relationship through other meticulous studies is needed in future investigations.

Implant failure needing reoperation and post-operative complications were evaluated in several studies.[20,23–25,27,30,33] The most common cause of reoperation was persistence of pre-operative symptoms (pain and functional impairment) likely to be caused by a mechanical failure of the device or non-integration of the scaffold with the remnant. The need for a second arthroscopy was usually very low, but in the study by Bulgheroni *et al*.,[25] 8 of the 28 patients underwent a new surgery for various conditions and 2 of them specifically had the implant removed and needed a HTO as an alternative. However, we remark that, where a control group was present,[20,23,24] for these last patients, the occurrence of reoperations or complications was higher or equivalent to that of those treated with the partial replacement. Detailed information about rates and related causes can be found in Table 4. No authors have so far reported any immunological reaction or disease transmission episodes, whereas serious events were reported more than once in different studies on transplant of total meniscus allograft.[44] This would recommend that scaffolds be used for partial meniscal implant as very safe and supposedly free from adverse immune reactions.

Imaging and histological findings regarding the evolution of the implanted scaffold and its effect on knee structures are provided in Table 6 and Table 7. Overall findings at plain radiography and MRI were always promising, indicating gradual integration of the scaffold with the remnant tissue, and often a decrease in progression of the signs of osteoarthritis on the chondral surfaces.[31,32] However, over time, the size of the implant decreased and its appearance worsened at long-term follow-up.[27] These findings were also confirmed at second-look arthroscopy, when performed. Genovese *et al*.[45] recently described different criteria to evaluate the status of the CMI on MRI, and several authors used them to assess the quality of the implant on imaging.[24,25,27,36]

A histological analysis of the tissue collected with later biopsies was performed in five studies.[23,25,28,29,31,32] They all showed the complete absence of inflammatory cells and markers while always referring that the scaffold was progressively invaded and replaced by new collagen and fibrochondrocytes organized in a tissue similar to the native meniscus. All the above-mentioned studies focused on biological scaffolds, so no conclusion on the evolution of the histology of the synthetic device can be currently drawn.

Partial meniscal replacement seems to have a significant beneficial effect also on patients who already had surgery on the meniscus, as reported by the only study[23] focusing on the impact of previous procedures and their effect on the following partial replacement. The authors concluded that patients suffering from a chronic meniscal injury already treated by surgery successfully regained significantly more of their lost activity than did the controls ($P = 0.02$), and they underwent significantly fewer non-protocol reoperations ($P = 0.04$). This was in contrast with patients suffering from an acute injury, who did not show significantly different outcomes when treated with CMI when compared with controls.

Another factor influential toward results of the procedure may be whether the lateral meniscus or the medial meniscus involved. Several studies focused only on the medial meniscus[20,23,24,26,27,29,31–33,35] or the lateral[36] meniscus, whereas others performed the procedure with no regards to the affected side,[30,34] all showing positive overall outcomes and all suggesting the partial replacement as an effective procedure. The only remarkable data were by Verdonk *et al.*,[33] who showed that a rate of implant failure doubled on the patients with lateral meniscal injury when compared with those receiving surgery on the medial side (three versus six failures out of nine total reoperations). The failures on the medial side were all related to the procedure, whereas five of six reoperations on the lateral meniscus were considered to have a possible or definite relationship with the scaffold. However, they considered any additional surgical procedure taking place during the 12-month relook arthroscopy as treatment failure in their analysis; therefore, the actual need for a reoperation cannot be precisely extrapolated by their data.

No study was yet designed to directly compare the results of the implant on the medial versus the lateral side, so more trials are needed to draw conclusion about this point.

Finally, we evaluated the methodological quality of the studies using CMS,[22] a validated system of criteria already adopted by authors of systematic reviews investigating many orthopaedic techniques and disorders.[22,46–52] The average Coleman score of 64.4 shows an overall moderately high methodological quality. Even if studies published on

this subject are mostly prospective and show acceptable methodology, only three studies[20,23,24] have a higher level of evidence (Level I or II) and only two studies[20,23] were randomized control trials. Most of the studies were case series,[25–36] therefore, providing conclusions supported by a low level of evidence because of their design.

Conclusion

Partial meniscal replacement using biological or synthetic scaffold is safe, and most of the published studies demonstrated remarkably good clinical outcomes, especially when compared with those obtained by controls undergoing partial meniscectomy. Post-operative clinical, radiological and histological assessments of the two devices approved for clinical use were equivalent. However, given their relatively recent development, there is a need for more and better designed randomized trials, to confirm with a stronger level of evidence the promising preliminary results achieved by the current research. Investigation of the several demographic and biomechanical factors that could influence the outcomes of this treatment, such as whether medial or lateral meniscus is affected, duration of the condition, prior knee surgeries, expected post-operative activity level, would also be essential to recommend this practice as completely effective.

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