Systematic Review

Resorbable Collagen Scaffolds for the Treatment of Meniscus Defects: A Systematic Review

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Purpose: The purpose of this study was to evaluate the clinical and structural outcomes after resorbable collagen meniscus scaffold implantation through a systematic review of the published literature. **Methods:** A systematic search of both the PubMed and Embase databases was undertaken to identify all studies that reported clinical and/or structural outcomes after resorbable collagen meniscus scaffold implantation for the treatment of defects involving either the medial or lateral meniscus. Extracted data included study characteristics; surgical methods and rehabilitation protocols; objective outcomes; and preoperative and postoperative subjective outcome scores including Lysholm, Tegner, International Knee Documentation Committee, and visual analog scale scores. **Results:** Thirteen studies were included in this review. There were 10 Level IV studies, 2 Level II studies, and 1 Level I study with follow-up intervals ranging from 3 months to 12.5 years. With a few exceptions, the study designs used in each study generally followed those which had been previously performed. Substantial differences in rehabilitation protocols and concomitant procedures were noted that may have had an effect on overall clinical outcomes. Objective findings were mostly consistent and typically showed minimal degenerative changes on postoperative radiographs, decreased signal intensity of the scaffold over time on magnetic resonance imaging, the presence of meniscus-like tissue at second-look arthroscopy, and good integration of new tissue as evidenced by histologic analysis of biopsy specimens. Most studies reported satisfactory clinical outcomes, and most patients showed substantial improvements in comparison with mean preoperative baseline values. **Conclusions:** On the basis of this systematic review, implantation of resorbable collagen scaffolds for the treatment of meniscus defects provides satisfactory clinical and structural outcomes in most cases. There is evidence that collagen meniscus scaffold implantation provides superior clinical outcomes when compared with partial meniscectomy alone. **Level of Evidence:** Level IV, systematic review of Level I, II, and IV studies.

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In recent years there has been an increased emphasis on meniscus-preserving treatments over partial or total meniscectomy because of a reported risk of degenerative changes in the tibiofemoral articular cartilage.[1-6] As a load is placed on the knee, the meniscus functions to convert axial loads into circumferentially oriented hoop stresses, thereby sparing the articular cartilage from excessive stress that may lead to arthritic changes.[7,8] When meniscus tissue is lost or damaged, increased peak and mean contact pressures are transmitted to the tibial plateau because of decreased meniscus contact areas and disruption of circumferential load-transmitting meniscus fibers.[9-11] Meniscus allograft transplantation and meniscus scaffold implantation have emerged as effective treatments to replace lost or damaged meniscus tissue and restore normal meniscus functional properties when repair is not possible.[12-14]

The indications for a meniscus tissue replacement procedure depend on the extent of tissue loss. Meniscus allograft transplantation is often recommended for younger patients after total or nearly total meniscectomy with neutral alignment, stable cruciate and collateral ligaments, unicompartmental activity-related pain and effusion, and no signs of significant arthritic changes in the affected compartment.[12] By contrast, implantation of a meniscus scaffold may be indicated for acute or irreparable meniscus injuries or after partial meniscectomy and requires at least a minimal rim of remaining meniscus tissue.[15-17]

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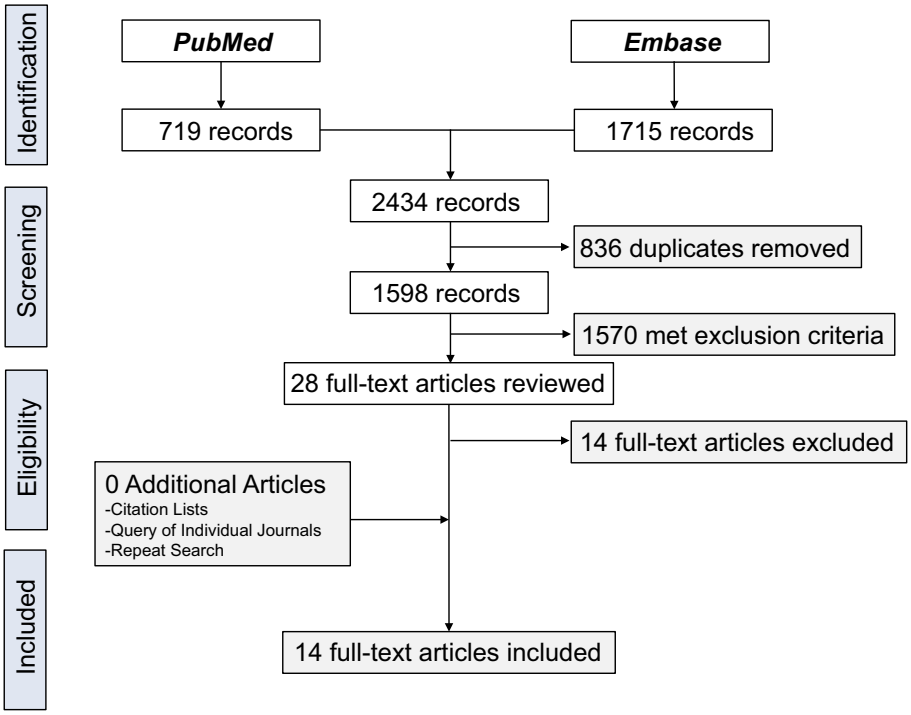

Fig 1. Flow diagram outlining sequence of literature retrieval.

Resorbable collagen meniscus scaffolds are made from processed bovine Achilles tendon tissue from which type I collagen fibers are extracted and later cross-linked with glutaraldehyde to form a matrix-like scaffold material. The resulting product is a flexible disk that can be trimmed and shaped to fit a meniscus defect. Before implantation, the damaged meniscus tissue and adjacent area are debrided to a vascular rim. Once the implantation site is prepared, the fitted implant is placed, allowing new cells to migrate and populate the scaffold. Over time, an organized healing response takes place, which ultimately results in restoration of meniscus structure and function. Phase I and phase II feasibility and safety trials have been successfully completed, followed by a multicenter, prospective randomized clinical trial that confirmed the safety and efficacy of the implant.[15,18] The purpose of this study was to evaluate the clinical and structural outcomes after resorbable collagen meniscus scaffold implantation through a systematic review of the published literature.

Methods

This study was performed according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19]

Literature Search

In March 2014 a systematic literature search was undertaken to identify all full-text studies of any language that (1) involved at least 4 human subjects and (2) reported clinical, structural, and/or microscopic outcomes after resorbable collagen meniscus scaffold implantation for the treatment of defects involving the medial and/or lateral meniscus of the knee. All other studies not meeting these criteria were excluded. Two reviewers independently queried both the PubMed and Embase databases using the search terms "collagen meniscus," "meniscus scaffold," and "meniscus implant." All records were screened by title and abstract, and after exclusion of duplicates and irrelevant records, the full text of all remaining studies was thoroughly reviewed for possible inclusion. The reference list for each of these articles was inspected for other relevant studies that were not retrieved by the initial database search. Major orthopaedic and musculoskeletal journals were also queried to identify relevant studies published within the most recent 6 months that had yet to be indexed. The search protocol was repeated at the end of this study to identify any new research that had become available between the time of the initial search and study completion.

Data Extraction

Two reviewers independently extracted article data including individual study characteristics, surgical methods and rehabilitation protocols, objective outcomes (second-look arthroscopy, imaging, and/or histologic data), and commonly reported preoperative and postoperative subjective outcome scores (Lysholm,

Tegner, International Knee Documentation Committee, and visual analog scale [VAS] scores).

Results

Literature Search and Study Selection

The initial literature search of both the PubMed and Embase databases identified 2,434 records from which 836 duplicates were removed, leaving a total of 1,598 unique records that were individually screened by title and abstract for relevance. This screening process identified 1,570 irrelevant records. The full-text articles of the remaining 28 records were reviewed in full. Fourteen of these full-text articles did not meet our inclusion criteria and were therefore removed. The remaining 14 full-text articles comprising 13 individual study protocols were included in this review.[13-15,17,18,20-28] No additional studies were found through manual search of reference lists, query of individual journal Web sites, or repeat search at the end of the study (Fig 1).

Study Characteristics

Table 1 presents a summary of individual study protocol characteristics. There were 674 patients in 10 Level IV studies, 2 Level II studies, and 1 Level I study with follow-up intervals ranging from a minimum of 3 months to a maximum of 152 months. The most commonly used outcomes measures were the Lysholm, Tegner, International Knee Documentation Committee, and VAS scores. Eleven of the 13 studies provided postoperative imaging data, 9 studies presented findings on second-look arthroscopy, and 5 studies obtained biopsy specimens for histologic analysis.

Table 2 summarizes the patient populations included in each study. Three of the 13 studies were comparative in nature: 2 of these studies compared meniscus scaffold implantation with partial medial meniscectomy,[13,14] and 1 study compared meniscus scaffold implantation with or without high tibial osteotomy.[21] Many of the inclusion and exclusion criteria were similar across multiple studies; however, there were a few differences. For example, Linke et al.[21] excluded patients with a body mass index greater than 25 kg/m^2, whereas Zaffagnini et al.[25] were the only investigators to include patients with lesions involving the lateral meniscus.

Table 3 outlines the specific surgical techniques, concomitant procedures, and rehabilitation protocols used in each study. Overall, many of the surgical techniques were similar with the exception of earlier studies performed by Stone et al.[18] and Linke et al.,[21] in which a mini-arthrotomy was performed to secure the meniscus scaffold to the adjacent capsular tissue. Nine studies reported concomitant procedures

Table 1. Summary of Individual Study Characteristics

Authors	Year	LOE	Total, N	Control, n	Scaffold, n	Follow-up, mo (range)	Outcome Scores Reported	Postoperative Imaging	Second-Look Arthroscopy	Histologic Analysis
Stone et al.[18]	1997	IV	9	0	9	Minimum of 3, 6, 12, 24, 36	Activity, overall knee	MRI/radiographs	Yes	Yes
Reguzzoni et al.[20]	2005	IV	4	0	4	Minimum of 6	None	None	Yes	Yes
Linke et al.[21]	2006	II	60	30	30	Minimum of 3, 12, 24	Lysholm, IKDC, VAS	None	Yes	No
Steadman and Rodkey[17*]	2005	IV	8	0	8	Mean, 69.6 (66-75.6)	Lysholm, Tegner, VAS	MRI	Yes	Yes
Genovese et al.[22]	2007	IV	40	0	40	Minimum of 6, 12, 24	None	MRI/MRA	Yes	No
Zaffagnini et al.[23]	2007	IV	8	0	8	Minimum of 3, 6, 12, 24; mean, 81.6 (72-96)	IKDC, Cincinnati	MRI/radiographs	Yes	No
Rodkey et al.[13]	2008	I	311	151	160	Mean, 59 (16-92)	Lysholm, Tegner, VAS	MRI	Yes	Yes
Bulgheroni et al.[24]	2010	IV	34	0	34	Minimum of 24, 60	Lysholm, Tegner	MRI/radiographs	Yes	Yes
Zaffagnini et al.[14]	2011	II	33	16	17	Mean, 133 (120-152)	Lysholm, Tegner, IKDC, VAS	MRI	No	No
Monllau et al.[26]	2011	IV	22	0	22	(121.2-150)	Lysholm	MRI/radiographs	No	No
Spencer et al.[27]	2012	IV	23	0	23	Mean, 24.1 (18-27)	Lysholm, Tegner, IKDC, KOOS	MRI	Yes	No
Zaffagnini et al.[25]	2012	IV	24	0	24	Minimum of 6, 24	Lysholm, Tegner, IKDC, VAS	MRI/radiographs	No	No
Hirschmann et al.[28]	2013	IV	60	0	60	Minimum of 12	Lysholm, Tegner, IKDC, VAS	MRI	No	No

IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; LOE, level of evidence; MRA, magnetic resonance arthrography; MRI, magnetic resonance imaging; VAS, visual analog scale.

*These data represent a continuation of the feasibility study first published in 1999 by Rodkey et al.[15]

Table 2. Summary of Patient Populations Included in Each Study

Authors	Interventions	Mean Age, yr (range)	Gender, M/F	Indications	Exclusion Criteria
Stone et al.[18]	Scaffold	39.3 (26-50)	8/2	Irreparable meniscus tear or major loss of medial meniscus tissue in stable knees	Previous collagen treatment, allergy to bovine collagen, concomitant injury to contralateral knee, inflammatory arthritis, severe degenerative joint disease
Reguzzoni et al.[20]	Scaffold	38 (24-50)	NR	Traumatic irreparable tears of posterior horn of medial meniscus	Identical to Stone et al.[18]
Linke et al.[21]	HTO *v* HTO + scaffold	41.6 (19-68)	NR	Acute or chronic subtotal loss of medial meniscus tissue with intact anterior and posterior horns and intact peripheral rim, biologically young and active patients, BMI <25 kg/m^2	Ligamentous instability, varus deformity >5°, advanced degenerative joint disease, scaffold for lateral meniscus, joint infection, allergy to bovine collagen
Steadman and Rodkey[17*]	Scaffold	40 (24-49)	8/0	Acute or chronic loss of one-third of native meniscus with ≥1 mm of intact tissue at periphery; all knees were stable at time of surgery	Total meniscus loss, full-thickness chondral defects, varus malalignment, inflammatory or systemic disease, known allergy to bovine collagen, pregnancy
Genovese et al.[22]	Scaffold	Median, 41 (23-58)	27/13	Irreparable lesions of medial meniscus (n = 28) or previous partial meniscectomy (n = 12)	NR
Zaffagnini et al.[23]	Scaffold	31 (20-51)	8/0	Acute irreparable medial meniscus tear (n = 3) or previous partial medial meniscectomy (n = 5); all knees were stable at time of surgery	Total meniscus loss, full-thickness chondral defects, inflammatory or systemic diseases, allergy to bovine collagen, pregnancy
Rodkey et al.[13]	Scaffold *v* partial medial meniscectomy	Scaffold: 39 Meniscectomy: 40	Scaffold: 126/35 Meniscectomy: 117/34	Irreparable injury or previous subtotal loss of medial meniscus with intact peripheral rim, neutral alignment, age <60 yr; all knees were stable or stabilized at time of surgery	Total meniscus loss, full-thickness chondral defects, PCL insufficiency, concomitant lesion involving >25% of lateral meniscus
Bulgheroni et al.[24]	Scaffold	39 (22-58)	25/9	Irreparable tear/defect involving >25% of medial meniscus, age <60 yr; all knees were stable or stabilized at time of surgery and HTO was performed when necessary	Full-thickness chondral defects, autoimmune disease, infection, other systemic diseases, allergy to animal collagen

(continued)

Table 2. Continued

Authors	Interventions	Mean Age, yr (range)	Gender, M/F	Indications	Exclusion Criteria
Zaffagnini et al.[14]	Scaffold *v* partial medial meniscectomy	Scaffold: 38 (24-60) Meniscectomy: 44 (28-60)	Scaffold: 17/0 Meniscectomy: 16/0	Irreparable acute medial meniscus tears requiring partial meniscectomy, chronic loss of >25% of medial meniscus, >1 mm of healthy tissue at rim of defect, <60 yr of age, healthy contralateral knee	Total meniscus loss, PCL insufficiency, full-thickness chondral defects, axial malalignment, allergy to animal collagen, systemic or local infection, history of anaphylaxis, corticosteroid use within 30 d before surgery, osteonecrosis, inability to complete rehabilitation, pregnancy
Monllau et al.[26]	Scaffold	42.3 (23.1-58.2)	20/5	Irreparable medial meniscus tear (n = 20) or previous "sizeable" meniscectomy (n = 5)	Identical to Steadman and Rodkey.[17]
Spencer et al.[27]	Scaffold	35 (17-47)	19/5	Current symptoms related to previous meniscectomy >12 mo before inclusion; all knees were stable, stabilized with ligament reconstruction, or realigned with HTO at time of surgery	Acute meniscus tears, full-thickness chondral defects (only in latter part of study)
Zaffagnini et al.[25]	Scaffold	36.3 (16.2-53.4)	20/4	Irreparable acute lateral meniscus lesions, irreparable chronic lesions involving >25% of lateral meniscus, >1 mm of intact meniscus tissue at rim of defect, 15-60 yr of age, contralateral healthy knee	Identical to Zaffagnini et al.[14]
Hirschmann et al.[28]	Scaffold	Medial: 35.5 (16-53) Lateral: 37.6 (17-54)	47/20	Previous subtotal medial (n = 55) or lateral (n = 12) meniscectomy	Previous total meniscectomy, instability, full-thickness chondral defects, allergy to animal collagen, known pregnancy

BMI, body mass index; F, female; HTO, high tibial osteotomy; M, male; NR, not reported; PCL, posterior cruciate ligament.
*These data represent a continuation of the feasibility study first published in 1999 by Rodkey et al.[15]

Table 3. Summary of Surgical Techniques, Concomitant Procedures, and Rehabilitation Protocols for Each Study

Authors	Surgical Technique	Concomitant Procedures	Rehabilitation Protocols
Stone et al.[18]	Removal of only irreparably damaged tissue was performed; a bleeding bed was created at the periphery; removed tissue was measured; and the collagen implant was trimmed, inserted through a 2-cm mini-arthrotomy incision, and secured in place with No. 2-0 PDS sutures.	ACL reconstruction: 2 ACL healing response: 2	NR
Reguzzoni et al.[20]	Identical to Stone et al.[18]	None reported	NR
Linke et al.[21]	Damaged medial meniscus was resected; the meniscus rim underwent trephination to create a bleeding bed at the periphery; the meniscus defect was measured arthroscopically; the scaffold was trimmed to the correct size; the scaffold was inserted through an arthroscopic "sleeve" and passed through a previously positioned suture loop; and No. 0 nonabsorbable sutures were tied vertically through the scaffold and the joint capsule using a 2 cm mini-arthrotomy incision.	None reported	CPM immediately postoperatively with application of knee brace restricted to 0°/0°/60° until week 4; brace loosened at week 4 to allow 0°/0°/90° of motion; non−weight bearing until week 6; "cycling" beginning at 3 mo, with unrestricted activities at 6 mo
Steadman and Rodkey[17*]	Identical to Stone et al.,[18] except that the scaffold was delivered through an arthroscopic cannula rather than a mini-arthrotomy incision; anterior and posterior margins were secured with horizontal mattress sutures; and the peripheral rim was secured with vertical mattress sutures spaced 4-5 mm apart. Transition from No. 2-0 absorbable to No. 2-0 nonabsorbable sutures occurred midway through the study.	None reported	Non−weight bearing in locked extension brace for 6 wk; brace removed 3-4 times/d for passive ROM exercises; ROM limited from 0°-60° for 4 wk and then 0°-90° until week 6; at 6 wk, brace unlocked and active and passive ROM exercises initiated; unrestricted activity at 6 mo
Genovese et al.[22]	NR	ACL reconstruction: 16 Microfracture: 2 (patella and MFC) ACI: 2 (MFC) HTO for varus deformity: 1	NR
Zaffagnini et al.[23]	Irreparable meniscus tissue was resected to a peripheral rim of healthy tissue; the peripheral rim underwent trephination with a microfracture awl to create a bleeding bed; the size of the meniscus defect was measured; the scaffold was trimmed according to the size of the meniscus defect; and between 2 and 6 No. 2-0 nonabsorbable sutures were used to secure the implant.	Microfracture: 1 (MFC)	CPM immediately postoperatively, cycled between 0° and 60° of flexion for 4 wk and subsequently increased to 90° until week 6; unlimited passive ROM allowed at week 6; non−weight bearing for first 6 wk postoperatively, with full weight bearing begun thereafter; unrestricted activity allowed after 6 mo

(continued)

Table 3. Continued

Authors	Surgical Technique	Concomitant Procedures	Rehabilitation Protocols
Rodkey et al.[13]	Scaffold: identical to Steadman and Rodkey[17*] Meniscectomy: identical to Steadman and Rodkey	Scaffold: ACL reconstruction: 47 Meniscectomy: ACL reconstruction: 38	Scaffold: identical to Steadman and Rodkey,[17*] except patients progressed from partial to full weight bearing between 2 and 6 wk postoperatively Meniscectomy: full weight bearing, unrestricted ROM, quadriceps and hamstring strengthening, activity as tolerated
Bulgheroni et al.[24]	Irreparable meniscus tissue was resected to a healthy, stable border; the peripheral rim was perforated to obtain a bleeding bed; the size of the defect was measured arthroscopically; the scaffold was trimmed and inserted through an arthroscopic cannula; and the scaffold was secured with No. 2-0 nonabsorbable sutures (horizontal mattress for anterior and posterior horns, vertical mattress for body and periphery).	ACL reconstruction: 11 HTO: 2 Microfracture: 1 (Outerbridge grade 3 on MFC)	Identical to Steadman and Rodkey,[17*] except knee brace was gradually discontinued after 8 wk
Zaffagnini et al.[14]	Scaffold: A full-thickness defect was created with a healthy rim of meniscus tissue; trephination of the peripheral rim was performed with a microfracture awl; the anterior and posterior meniscus attachment sites were trimmed; the meniscus defect was measured arthroscopically; the scaffold was trimmed according to the size of the meniscus defect; and the scaffold was inserted through an arthroscopic cannula and sutured to the peripheral host remnant using an inside-out technique with No. 2-0 nonabsorbable suture (vertical stitches every 5 mm and horizontal stitches at the anterior and posterior attachment sites). Meniscectomy: same as above, except scaffold was not prepared or inserted	Scaffold: ACL reconstruction: 2 Meniscectomy: ACL reconstruction: 2	Scaffold: non–weight bearing for 2 wk followed by progressive increase in weight bearing as tolerated; locked extension brace for initial 6 wk postoperatively; brace removed 3-4 times/d for passive ROM exercises; ROM limited from 0°-60° initially and increased to 0°-90° as tolerated; isokinetic strengthening began on day 2 postoperatively; cycling began at 2 wk and isotonic strengthening at 4 wk, with full activities at 6 mo Meniscectomy: identical to Rodkey et al.[13]

(continued)

Table 3. Continued

Authors	Surgical Technique	Concomitant Procedures	Rehabilitation Protocols
Monllau et al.[26]	Irreparable medial meniscus tissue was removed to a stable rim of healthy tissue; puncture holes were made through the meniscus rim using an 18-gauge spinal needle or microfracture awl; the defect size was measured arthroscopically; the scaffold was trimmed according to the defect size; the MCL was released percutaneously to allow enlargement of the anteromedial portal and to facilitate scaffold insertion; the scaffold was sutured using an inside-out technique (vertical sutures every 4-5 mm along meniscus rim, horizontal sutures at anterior and posterior attachment sites); and a 3- to 4-cm longitudinal incision was made to retrieve the suture devices securing the posterior aspect of the implant.	ACL reconstruction: 20 Microfracture: 1 (Outerbridge grade 3 on MFC)	Quadriceps and hamstring "exercises" were begun immediately postoperatively. Passive ROM was restricted to between 0° and 60° of flexion up to 3 wk, at which point passive ROM was gradually increased to 90° until 6 wk when unrestricted passive ROM was allowed. All patients were non−weight bearing for the initial 2 wk postoperatively. Weight bearing was progressively increased between weeks 3 and 8 until full weight bearing was achieved. Unrestricted activities were allowed at 6 mo depending on patient progress.
Spencer et al.[27]	Irreparable meniscus tissue was debrided to vascular tissue; the defect was shaped to create a 90° angle at the posterior and anterior edges using an arthroscopic punch; the meniscus rim underwent trephination with a microfracture awl; the length of the defect was measured arthroscopically; a value of 10% was added to the length of the defect to allow a snug fit of the scaffold; percutaneous MCL release was occasionally performed to facilitate scaffold insertion; and the scaffold was secured using an inside-out or all-inside technique.	Ligament reconstruction: 1 ACL, 1 LCL Osteotomy: 1 HTO, 1 DFO Microfracture: 1 (tibial plateau)	A hinged knee brace was applied immediately postoperatively. The brace restricted ROM to 30° of flexion during the first 2 wk with a gradual increase to 90° at 6 wk and to full flexion at 12 wk. Weight bearing was gradually introduced throughout rehabilitation, and full weight bearing was achieved between 8-10 wk. A return to "light" sporting activities was allowed at 6 mo, with unrestricted sporting activities at 12 mo.
Zaffagnini et al.[25]	Identical to Zaffagnini et al.,[14] except all procedures were performed on lateral meniscus	ACL reconstruction: 4 Microfracture: 6 (lateral tibial plateau) ACL cyst removal: 1	Identical to scaffold group in article by Zaffagnini et al.[14]
Hirschmann et al.[28]	Irreparable meniscus tissue was resected to a stable base; the base underwent trephination with a needle to induce bleeding; the size of the defect was measured arthroscopically; the scaffold was trimmed according to the defect size; the scaffold was inserted and secured using an all-inside technique; and lesions of the anterior horn were fixed by an inside-out technique.	ACL reconstruction: 45 HTO: 5 Microfracture: 3	NR

ACI, autologous chondrocyte implantation; ACL, anterior cruciate ligament; CPM, continuous passive motion; DFO, distal femoral osteotomy; HTO, high tibial osteotomy; LCL, lateral collateral ligament; MCL, medial collateral ligament; MFC, medial femoral condyle; NR, not reported; PDS, polydioxanone sulfate; ROM, range of motion.

*These data represent a continuation of the feasibility study first published in 1999 by Rodkey et al.[15]

Table 4. Summary of Findings on Imaging Studies, Second-Look Arthroscopy, and Histologic Analysis

	Radiography		MRI		Second-Look Arthroscopy		Light Microscopy	
Authors	No. of Patients	Findings	No. of Patients	Findings	No. of Patients	Findings	No. of Patients	Findings
Stone et al.[18]	9	36 mo: no change in joint space	9	Up to 36 mo: progressive tissue ingrowth	6	6 mo: similar in appearance to normal meniscus fibrocartilage	9	3 mo (n = 3): substantial portion of scaffold remained; no evidence of new fibrocartilage 6 mo (n = 6): more collagen; primarily immature chondroid
Reguzzoni et al.[20]	—	NR	—	NR	4	6 mo: regeneration of meniscus-like tissue with implant healing to capsule and residual meniscus stump; chondral surfaces intact	4	6 mo: scaffold visible but invaded with fibroblast-like cells and extracellular matrix
Linke et al.[21]	—	NR	—	NR	23	8-18 mo: scaffold completely healed in 8; partially healed in 7; small portion of scaffold remaining in 7; 1 other patient required resection of scaffold	—	NR
Steadman and Rodkey[17*]	8	24 mo: no change in joint space; no progression of Fairbanks changes Mean, 70 mo (range, 66-75 mo): no progression of degeneration	8	24 mo: progressive decrease in signal intensity over time Mean, 70 mo (range, 66-75 mo): continued decrease in signal intensity; more closely resembled native meniscus tissue	8	6 mo (n = 6): new tissue regeneration in all patients; variable degree of maturity; stable interface with host meniscus rim 12 mo (n = 2): more mature appearance than biopsy specimens obtained at 6 mo; gross evidence of new tissue generation Mean, 70 mo (range, 66-75 mo) (n = 8): Outerbridge grade slightly worsened in 2 patients; others either improved or remained unchanged	8	6 mo (n = 6) and 12 mo (n = 2): progressive invasion and replacement of scaffold with meniscus-like cells Minimum, 66 mo (n = 3): fibrocartilaginous tissue with uniform extracellular matrix

(continued)

Table 4. Continued

	Radiography		MRI		Second-Look Arthroscopy		Light Microscopy	
Authors	No. of Patients	Findings	No. of Patients	Findings	No. of Patients	Findings	No. of Patients	Findings
Genovese et al.[22]	—	NR	40	6 and 12 mo: high signal intensity in scaffold 24 mo (n = 16): significantly decreased signal intensity; 4 patients with new chondral defect; complete scaffold resorption in 1 patient	12	24 mo: progressive reduction of scaffold size in posterior horn region (from 25%-90%); complete resorption of scaffold in 1 patient	12	Details not specified
Zaffagnini et al.[23]	8	Minimum, 72 mo: progression of degenerative changes in 2 patients when compared with 24-mo radiographs	8	Minimum, 72 mo: myxoid degeneration of scaffold in 5 patients; decreased scaffold size in 2 patients; complete scaffold resorption in 1 patient	3	Minimum, 24 mo: 2 patients had new tissue but smaller volume than initial scaffold size; minimal new tissue in third patient; cartilage degeneration remained unchanged	—	NR
Rodkey et al.[13]	—	NR	—	NR	141	12 mo: new tissue well integrated with host meniscus rim; similar feel to normal meniscus; no new chondral damage was evident; significant increase in tissue surface area		12 mo: evidence of scaffold infiltration with maturing fibrous connective tissue; cells seen directly apposed to scaffold surface
Bulgheroni et al.[24]	28	Minimum, 60 mo: no degenerative changes in 18 of 28 patients (64.3%); degenerative changes in 10 of 28 patients (35.7%)	28	Minimum, 24 and 60 mo: all MRI studies at both 24 and 60 mo showed increased signal intensity when compared with normal meniscus; signal intensity decreased over time	8	Mean, 19.3 mo (range, 7-60 mo): new tissue within scaffold but scaffold reduced in size compared with original scaffold size	8	Mean, 19.3 mo (range, 7-60 mo): meniscus-like tissue with "several cells and some vessels"; lacunae between scaffold fibers filled with connective tissue; no phagocytes or macrophages observed
Zaffagnini et al.[14]	17	Minimum, 120 mo: no joint space narrowing in scaffold group; decreased joint space in meniscectomy group	17	Minimum, 120 mo: myxoid degeneration of scaffold in 11; normal signal and reduced scaffold size in 4; no recognizable implant in 2	—	NR	—	NR

(continued)

Table 4. Continued

Authors	Radiography		MRI		Second-Look Arthroscopy		Light Microscopy	
	No. of Patients	Findings	No. of Patients	Findings	No. of Patients	Findings	No. of Patients	Findings
Monllau et al.[26]	23	Minimum, 120 mo: increased degenerative changes in 5 patients after scaffold at final follow-up	19	Minimum, 12 mo (n = 10) and 120 mo (n = 19): All cases showed decreased volume of the scaffold at final follow-up; 12 of 19 patients had increased signal intensity of the scaffold at final follow-up when compared with earlier studies.	—	NR	—	NR
Spencer et al.[27]	—	NR	20	Mean, 19 mo (range, 6-36 mo): mixed appearance of new tissue (varied from good integrity to marked erosion); MRI findings did not suggest differentiation into fibrocartilage	14	Mean, 12.8 mo: variable amounts of regenerative tissue; 9 of 14 had <50% defect fill	—	NR
Zaffagnini et al.[25]	24	Mean, 26.0 ± 2.2 mo: results not provided	24	Mean, 26.0 ± 2.2 mo: scaffold identical to normal meniscus in 3; small and irregular scaffold in 18; scaffold completely resorbed in 3	—	NR	—	NR
Hirschmann et al.[28]	—	NR	60	Minimum, 12 mo: scaffold completely preserved in 2; scaffold partially resorbed in 55; scaffold completely resorbed in 3	—	NR	—	NR

MRI, magnetic resonance imaging; NR, not reported.
*These data represent a continuation of the feasibility study first published in 1999 by Rodkey et al.[15]

including ligament reconstruction procedures, autologous chondrocyte implantation, high tibial osteotomy, and microfracture. The reported rehabilitation protocols varied significantly across each study, specifically regarding the use and duration of continuous passive motion, the use and position of knee braces, and the duration of non–weight-bearing status postoperatively. Four studies did not report a specific rehabilitation protocol.

Objective Outcomes

Table 4 summarizes the objective findings reported by each study. Whereas most of the 7 studies that reported postoperative radiographic findings indicated minimal to no degenerative changes, Bulgheroni et al.[24] noted degenerative changes in 10 of 28 patients (35.7%) after a minimum 60-month follow-up period. Overall, findings on magnetic resonance imaging (MRI) studies showed high signal intensity at the site of scaffold implantation; however, this finding appeared to diminish in studies that reported longer follow-up periods. Several studies also found that the meniscus scaffold decreased in volume over time. Second-look arthroscopy showed the presence of newly formed meniscus-like tissue in the area of the scaffold with an overall decrease in the original size of the scaffold in studies that obtained biopsy specimens postoperatively. Histologic analysis most often showed good tissue integration and increasing degrees of meniscus fibrochondrocyte maturation as the follow-up period increased. None of the studies reported evidence of tissue rejection.

Subjective Outcomes

Tables 5 and 6 provide the most commonly reported clinical outcome scores for each study. Each study that reported clinical outcomes indicated statistically significant improvements in postoperative outcome scores when compared with preoperative baseline values. A summary of the authors' conclusions is presented in Table 7.

Discussion

In this study a systematic literature search identified 14 studies that evaluated the clinical, structural, and/or microscopic outcomes after implantation of resorbable meniscus scaffolds for the treatment of lesions involving the medial or lateral meniscus. With a few exceptions, each study design generally followed those which had been previously performed. However, there were significant differences in rehabilitation protocols and concomitant procedures across each study that may have had an effect on clinical outcomes. Objective findings were generally consistent and showed minimal degenerative changes on radiographs; diminishing signal intensity of the scaffold over time on MRI, indicating an ongoing maturation

Table 5. Summary of Outcome Scores for All Comparative Studies Included in Review

Authors	LOE	Year	Groups	N	Final Follow-up, mo	Lysholm Score			IKDC Score			VAS Score		
						Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ
Linke et al.[21]	II	2006	HTO + scaffold	23	Minimum, 24	65.2	93.6	+28.4	60.3	83.0	+22.7	4.9	2.2	−2.7
			HTO	16	Minimum, 24	67.0	91.0	+24.0	53.0	77.0	+24.0	5.2	1.5	−3.7
Rodkey et al.[13]	I	2008	Acute											
			Scaffold	75	Mean, 64 (range, 23-89)	64	90	+26				2.1	0.5	−1.6
			Meniscectomy	82	Mean, 60 (range, 16-85)	59	87	+28				2.7	0.6	−2.1
			Chronic											
			Scaffold	82	Mean, 60 (range, 23-90)	63	79	+16				3.7	1.9	−1.8
			Meniscectomy	69	Mean, 57 (range, 23-92)	56	78	+22				3.9	2.1	−1.8
Zaffagnini et al.[14]	II	2011	Scaffold	17	Minimum, 120							6.0	1.2	−4.8
			Meniscectomy	16	Minimum, 120							7.0	3.3	−3.7

NOTE. A delta (Δ) indicates the preoperative to postoperative change in the outcome score.
HTO, high tibial osteotomy; IKDC, International Knee Documentation Committee; LOE, Level of Evidence; Post, postoperative; Pre, preoperative; VAS, visual analog scale.

process of the new tissue; the presence of meniscus-like tissue on direct visualization at second-look arthroscopy; and good integration of new meniscus tissue on histologic analysis. Most studies reported satisfactory clinical outcomes, and most patients showed substantial improvements in comparison with mean preoperative baseline values.

One of the primary goals of collagen meniscus scaffold implantation is to restore a normal volume of meniscus tissue that allows for the transmission and distribution of normal physiological shear and compressive forces over the weight-bearing articular surfaces. Several of the studies included in this review showed a progression of meniscus-like tissue regeneration within the implanted scaffold through MRI studies, observations on second-look arthroscopy, and histologic analysis. In general, MRI studies showed increased signal intensity early in the postoperative period that appeared to diminish with longer-term follow-up. Some authors also reported some resorption of the collagen scaffold that resulted in a decreased final meniscus volume. The clinical relevance of this resorption has not yet been evaluated; however, resorption did not appear to affect the reported clinical outcomes within the individual study periods. Second-look arthroscopy most often showed evidence of new tissue ingrowth and, in some cases, decreased size of the implant—new tissue complex. In many of these studies, biopsy specimens were also obtained during second-look arthroscopy to evaluate the histologic appearance of the newly formed tissue. Stone et al.[18] obtained biopsy specimens from a total of 9 patients at 3 months (n = 3) and 6 months (n = 6) postoperatively. Although different patients were evaluated at each time point, their results indicate that new meniscus fibrocartilage does not form until greater than 3 months postoperatively, which may have significant implications regarding the progression of rehabilitation. Steadman and Rodkey[17] obtained biopsy specimens in 8 patients at both 6 months (n = 6) and 12 months (n = 2) postoperatively. Histologic analysis showed a progressive invasion of the implant with meniscus-like cells at both time points. They also obtained biopsy specimens from 3 other patients a minimum of 66 months after the index surgery, which showed a continuous, uniform fibrocartilaginous matrix. Other authors have found similar results with longer-term follow-up in larger cohorts.[13,14]

A second goal of collagen meniscus scaffold implantation is to prevent further degenerative changes associated with the loss of meniscus tissue. Both Zaffagnini et al.[25] and Monllau et al.[26] obtained radiographs at approximately 120 months postoperatively and noted only a few patients with degenerative changes. Several other authors have obtained similar results. However, of the 6 studies that reported postoperative radiographic

Table 6. Overall Clinical Outcome Scores Obtained at Final Follow-up for All Level IV Studies

Authors	N	Final Follow-up, mo	Lysholm Score			Tegner Score			VAS Score*		
			Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ
Stone et al.[18]	9	Minimum, 36									
Reguzzoni et al.[20]	4	Minimum, 6	62.3 (41-70)	93.8 (82-100)	+31.5	2.3 (2-3)	4.5 (4-5)	+2.2			
Steadman and Rodkey[17]†	8	Mean, 69.6 (range, 66-75.6)	75 (52-97)	88 (74-95)	+13	3.4 (1-5)	6.0 (4-8)	+2.6	2.3 (0-3.4)	1.1 (0-5.3)	−1.2
Genovese et al.[22]	40	Minimum, 24									
Zaffagnini et al.[23]	8	Mean, 81.6							5.1 (2-7)	1.8 (1-3)	−3.3
Bulgheroni et al.[24]	34	Minimum, 60	58	93	+35	2	5	+3			
Monllau et al.[26]	22	Minimum, 120	59.9 (30-90)	87.6 (59-100)	+27.7				5.5 (2-8)	2.0 (0-6)	−3.5
Spencer et al.[27]	23	Mean, 19.4 (range, 12-27)	59.2‡	84.2‡	+25.0	3.8 ‡	4.9 ‡	+1.1			
Zaffagnini et al.[25]	24	Minimum, 24	64.0 ± 16.2	92.7 ± 13.8	+28.7	3 (2-4)§	5 (4-7)§	+2	5.5 ± 2.9	1.9 ± 2.6	−3.6
Hirschmann et al.[28]	55	Minimum, 12	68 ± 20	93 ± 9	+25	3 (0-8)	6 (2-10)	+3	4.4 ± 3.1	2.0 ± 1.1	−2.4

NOTE. A delta (Δ) indicates the preoperative to postoperative change in the outcome score. Preoperative and postoperative scores are presented as mean, mean (range), or mean ± SD unless otherwise indicated.

Post, postoperative; Pre, preoperative; VAS, visual analog scale.

*Scores were converted from a 100-point scale to a 10-point scale where necessary.

†These data represent a continuation of the feasibility study first published in 1999 by Rodkey et al.[15]

‡Weighted mean values were derived from sample sizes and confidence intervals reported in the original study. Information needed to compute pooled standard deviations was not available.

§Data in parentheses represent the interquartile range.

Table 7. Summary of Authors' Conclusions

Authors	Authors' Conclusions
Stone et al.[18]	MRI studies showed maturation of signal within the regenerated meniscus at 3, 6, 12, and 36 mo postoperatively.
Reguzzoni et al.[20]	Collagen meniscus implants provide a scaffold on which marrow precursors can form fully functional tissue.
Linke et al.[21]	Study conclusions were not stated.
Steadman and Rodkey[17]	Collagen meniscus implantation resulted in the development of meniscus-like tissue with maintenance of structure and function >5 yr postoperatively.
Genovese et al.[22]	Structural features of collagen meniscus implants can be monitored with MRI for ≥2 yr postoperatively. MRI with contrast is preferred at the first follow-up visit to allow for early identification of chondral defects.
Zaffagnini et al.[23]	Highly satisfactory results after collagen meniscus implantation were found between 6 and 8 yr postoperatively.
Rodkey et al.[13]	Collagen meniscus implants support the ingrowth of new tissue that appears to improve clinical outcomes in patients with chronic meniscus injuries. The newly formed tissue appears to be biomechanically stable for ≥5 yr.
Bulgheroni et al.[24]	The 5-yr results are encouraging for patients with irreparable medial meniscus tears after partial meniscectomy involving >25% of the meniscus and in patients who have persistent pain after meniscectomy.
Zaffagnini et al.[14]	When compared with partial medial meniscectomy alone, collagen meniscus implantation resulted in improved pain, activity level, and radiologic outcomes after a minimum 10-yr follow-up period.
Monllau et al.[26]	Collagen meniscus implantation provided significant pain relief and functional improvement after a minimum 10-yr follow-up period. There was a low rate of long-term implant failure.
Spencer et al.[27]	Treatment with meniscus scaffolds can provide good pain relief after partial meniscectomy.
Zaffagnini et al.[25]	Collagen meniscus implantation for lateral meniscus deficiency resulted in decreased pain and improved function in 96% of patients and "excellent/good" Lysholm scores in 87% of patients after a minimum 2-yr follow-up period.
Hirschmann et al.[28]	Excellent clinical results were obtained after collagen meniscus implantation 1 yr postoperatively in highly active patients as evidenced by significant pain relief and functional improvement.

MRI, magnetic resonance imaging.

findings, only the study by Bulgheroni et al.[24] noted substantial degenerative changes in a large proportion of the study cohort (10 of 28 patients, 35.7%) after a 60-month follow-up period. Thorough evaluation of their study did not show any obvious reasons for the increased rate of degenerative changes when compared with the other studies included in our review.

Another goal of collagen meniscus scaffold implantation is to provide improved long-term patient outcomes when compared with partial meniscectomy. Within this review, 2 comparative studies were identified that evaluated the clinical outcomes after either partial meniscectomy or collagen meniscus scaffold implantation.[13,14] After a follow-up interval of 10 years, Zaffagnini et al.[14] reported a statistically significant improvement in both Tegner and VAS scores in patients treated with a collagen meniscus scaffold when compared with those who underwent partial meniscectomy alone. Rodkey et al.[13] showed no differences in clinical outcomes between partial medial meniscectomy and meniscus scaffold implantation in patients with acute injuries to the medial meniscus; however, patients with chronic injuries who were treated with a collagen meniscus scaffold were found to have regained a significantly greater proportion of their lost activity when compared with those who underwent partial medial meniscectomy alone ($P = .02$). Although those patients with chronic injuries had decreased overall outcome scores when compared with those with acute injuries, both groups showed statistically significant improvements in outcome scores when compared with preoperative baseline values.

Limitations

There are several limitations that are inherent to this particular study design. First, the conclusions made in this study are primarily based on Level IV studies and may not be directly applicable to all clinical situations. Second, although risk-of-bias assessments are standard practice for systematic reviews, we chose to exclude this assessment because our institution is connected with several of the included studies. Third, we were unable to perform a meta-analysis of the clinical results of collagen meniscus scaffold implantation because of differing study methodologies and data reporting across each study. Finally, we did not attempt to make any comparisons between resorbable collagen scaffolds and any other implants or devices.

Conclusions

On the basis of this systematic review, implantation of resorbable collagen scaffolds for the treatment of meniscus defects provides satisfactory clinical and structural outcomes in most cases. There is evidence that collagen meniscus scaffold implantation provides superior clinical outcomes when compared with partial meniscectomy alone.

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References

1. Jackson JP. Degenerative changes in the knee after meniscectomy. *BMJ* 1968;2:525-527.
2. Jørgensen U, Sonne-Holm S, Lauridsen F, Rosenklint A. Long-term follow-up of meniscectomy in athletes. A prospective longitudinal study. *J Bone Joint Surg Br* 1987;69:80-83.
3. Maletius W, Messner K. The effect of partial meniscectomy on the long-term prognosis of knees with localized, severe chondral damage. A twelve- to fifteen-year followup. *Am J Sports Med* 1996;24:258-262.
4. Pengas IP, Assiotis A, Nash W, Hatcher J, Banks J, McNicholas MJ. Total meniscectomy in adolescents: A 40-year follow-up. *J Bone Joint Surg Br* 2012;94:1649-1654.
5. Scheller G, Sobau C, Bülow JU. Arthroscopic partial lateral meniscectomy in an otherwise normal knee: Clinical, functional, and radiographic results of a long-term follow-up study. *Arthroscopy* 2001;17:946-952.
6. Stein T, Mehling AP, Welsch F, von Eisenhart-Rothe R, Jäger A. Long-term outcome after arthroscopic meniscal repair versus arthroscopic partial meniscectomy for traumatic meniscal repairs. *Am J Sports Med* 2010;38:1542-1548.
7. Ghosh P, Taylor TK. The knee joint meniscus. A fibrocartilage of some distinction. *Clin Orthop Relat Res* 1987;224:52-63.
8. Seitz AM, Lubomierski A, Friemert B, Ignatius A, Dürselen L. Effect of partial meniscectomy at the medial posterior horn on tibiofemoral contact mechanics and meniscal hoop strains in human knees. *J Orthop Res* 2012;30:934-942.
9. Allaire R, Muriuki M, Gilbertson L, Harner CD. Biomechanical consequences of a tear of the posterior root of the medial meniscus. Similar to total meniscectomy. *J Bone Joint Surg Am* 2008;90:1922-1931.
10. Bedi A, Kelly NH, Baad M, et al. Dynamic contact mechanics of the medial meniscus as a function of radial tear, repair, and partial meniscectomy. *J Bone Joint Surg Am* 2010;92:1398-1408.
11. Ode GE, Van Thiel GS, McArthur SA, et al. Effects of serial sectioning and repair of radial tears in the lateral meniscus. *Am J Sports Med* 2012;40:1863-1870.
12. LaPrade RF, Wills NJ, Spiridonov SI, Perkinson S. A prospective outcomes study of meniscal allograft transplantation. *Am J Sports Med* 2010;38:1804-1812.
13. Rodkey WG, DeHaven KE, Montgomery WH III, et al. Comparison of the collagen meniscus implant with partial meniscectomy. A prospective randomized trial. *J Bone Joint Surg Am* 2008;90:1413-1426.
14. Zaffagnini S, Marcheggiani Muccioli GM, Lopomo N, et al. Prospective long-term outcomes of the medial collagen meniscus implant versus partial medial meniscectomy: A minimum 10-year follow-up study. *Am J Sports Med* 2011;39:977-985.
15. Rodkey WG, Steadman JR, Li ST. A clinical study of collagen meniscus implants to restore the injured meniscus. *Clin Orthop Relat Res* 1999;367:S281-S292 Suppl.
16. Steadman JR, Rodkey WG, Li ST. The collagen meniscus implant: Development and clinical trials of a device to treat meniscus injuries of the knee. *Sport Orthop Traumatol* 2000;16:173-177.
17. Steadman JR, Rodkey WG. Tissue-engineered collagen meniscus implants: 5- to 6-year feasibility study results. *Arthroscopy* 2005;21:515-525.
18. Stone KR, Steadman JR, Rodkey WG, Li ST. Regeneration of meniscal cartilage with use of a collagen scaffold. Analysis of preliminary data. *J Bone Joint Surg Am* 1997;79:1770-1777.
19. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analysis: The PRISMA statement. *PLoS Med* 2009;6:e1000097.
20. Reguzzoni M, Manelli A, Ronga M, Raspanti M, Grassi FA. Histology and ultrastructure of a tissue-engineered collagen meniscus before and after implantation. *J Biomed Mater Res B Appl Biomater* 2005;74:808-816.
21. Linke RD, Ulmer M, Imhoff AB. Replacement of the meniscus with a collagen implant (CMI). *Oper Orthop Traumatol* 2006;18:453-462 [in German].
22. Genovese E, Angeretti MG, Ronga M, et al. Follow-up of collagen meniscus implants by MRI. *Radiol Med* 2007;112:1036-1048.
23. Zaffagnini S, Giordano G, Vascellari A, et al. Arthroscopic collagen meniscus implant results at 6 to 8 years follow up. *Knee Surg Sports Traumatol Arthrosc* 2007;15:175-183.
24. Bulgheroni P, Murena L, Ratti C, Bulgheroni E, Ronga M, Cherubino P. Follow-up of collagen meniscus implant patients: Clinical, radiological, and magnetic resonance imaging results at 5 years. *Knee* 2010;17:224-229.
25. Zaffagnini S, Marcheggiani Muccioli GM, Bulgheroni P, et al. Arthroscopic collagen meniscus implantation for partial lateral meniscal defects: A 2-year minimum follow-up study. *Am J Sports Med* 2012;40:2281-2288.
26. Monllau JC, Gelber PE, Abat F, et al. Outcome after partial medial meniscus substitution with the collagen meniscal implant at a minimum of 10 years' follow-up. *Arthroscopy* 2011;27:933-943.
27. Spencer SJ, Saithna A, Carmont MR, Dhillon MS, Thompson P, Spalding T. Meniscal scaffolds: Early experience and review of the literature. *Knee* 2012;19:760-765.
28. Hirschmann MT, Keller L, Hirschmann A, et al. One-year clinical and MR imaging outcome after partial meniscal replacement in stabilized knees using a collagen meniscus implant. *Knee Surg Sports Traumatol Arthrosc* 2013;21:740-747.