Meniscus Reconstruction: the new field of rebuilding meniscus cartilage

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Introduction

The collagen meniscus implant for meniscus cartilage "tissue repair" opened a new field of meniscus reconstruction. Tears of the meniscus cartilage that were previously treated with meniscectomy can now be augmented with a collagen scaffold and growth factors or stem cells in an effort to re-grow lost tissue and extend meniscus repair options (Fig 1). This monograph describes the development of the collagen scaffold and presents five cases of meniscus reconstruction using a collagen regeneration template. The purpose of this monograph is to stimulate ideas for this new field of meniscus reconstruction. We do not however have sufficient numbers to make recommendations.

The collagen meniscus implant: what is it? The collagen meniscus implant is a lyophilized Type I collagen scaffold made from solubilized bovine Achilles tendon, uniquely crosslinked with a combination of glycosaminoglycans (GAGs) and low-level aldehyde. The strategy of crosslinking collagen with GAGs serves to simulate the chemical environment of the native meniscus cartilage and promote migration of fibrochondrocytes from the periphery into the collagen scaffold. Crosslinking of the collagen also helps slow the degradation of the scaffold. For example, an un-crosslinked scaffold such as a hemostatic sponge would be 50% degraded in a collagenase bath in 24 hours compared to a crosslinked scaffold which takes three weeks to degrade by 50% in a similar solution. The preservation of the structure through crosslinking permits the device to act as a regeneration template for re-growth of new tissue.

The development of the collagen meniscus implant started in 1984 through the senior author's efforts in finding a way to replace the meniscus cartilage. After two years of researching the known material properties, it was concluded that existing materials were not satisfactory for replacement. The meniscus absorbs 1-5 times body weight at 2-3 million cycles per year. No artificial material was soft enough, durable enough and lubricious enough to withstand the forces in the knee without damaging the opposing articular cartilage. Once it was determined that artificial materials were not suitable to replace the meniscus, the focus shifted to developing methods for regrowth of meniscus cartilage using a regeneration template. Working with Shu-Tung Li, PhD, and building on technology developed by Ioannis V. Yannas, PhD at MIT for skin repair, the author designed and built the

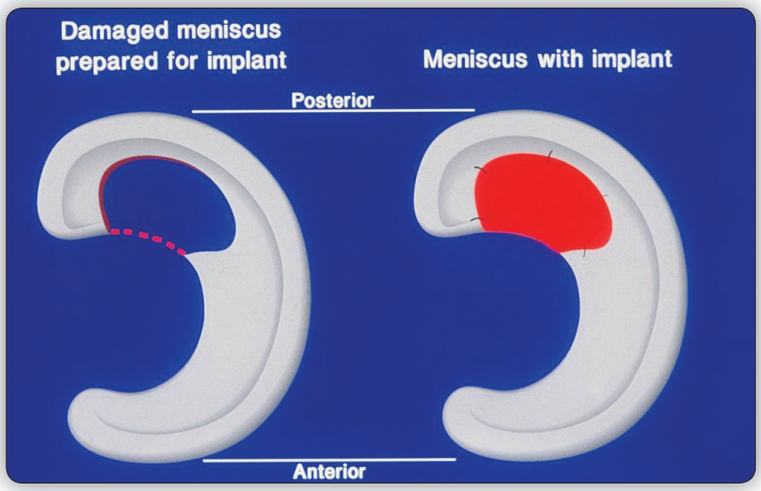

Fig. 1.
Illustration of medial meniscus defect and meniscus with collagen meniscus implant

crosslinked collagen scaffold that became the collagen meniscus implant in 1986. The implant was first tested in collaboration with Richard Webber, PhD and demonstrated that meniscus fibrochondrocytes in tissue culture would grow into the scaffold. The scaffold was tested as a meniscus regeneration template, a cervical disc regeneration template, an articular cartilage implant and an ACL repair device from 1986 until 1990. Funding by the Letterman Army Institute of Research led to animal trials conducted in collaboration with Phil Bowman, PhD; LuAnn McKinney, DVM; and Bill Rodkey, DVM. Funding was limited to testing of the scaffold for meniscus regeneration, although other areas of application showed promise. The FDA approved a Phase-I clinical feasibility trial of the device as a meniscus template in ten patients, which was successfully completed in San Francisco in 1997. In 1999 the Phase-II clinical trial was completed in Vail Colorado with similar results. Under an FDA Investigational Device Exemption (IDE), a prospective, randomized, multicenter, controlled clinical trial was completed in 2008. A 510(k) approval of the device was issued by the FDA in 2009 however it was rescinded in 2010 after concluding that there was insufficient data to support the approval.

While over 4,000 collagen meniscus implants have been performed in Europe since its approval in 2000, the FDA process in the US became quite convoluted. (Note: the senior author of this article (KRS) completed the first clinical trial and was not involved in the subsequent clinical trials or FDA processes and founded but is not involved with the sponsor company). The results of the initial clinical trials were difficult to interpret due to the lack of objective outcome measures for meniscus reconstruction (a ligament is a binary evaluation, while methods of objective determination of the degree and efficacy of meniscus regeneration is not well established). Additionally, the sponsor company, ReGen Biologics Inc., decided to pursue the 510(k) pathway, which permits faster approval if a substantially equivalent 510(k) device is already legally marketed. The company abandoned the nearly completed IDE trial and applied for 510(k) approval, which it received in December 2008 for use in the medial meniscus. The approval process became the subject of media, and subsequently congressional, attention and

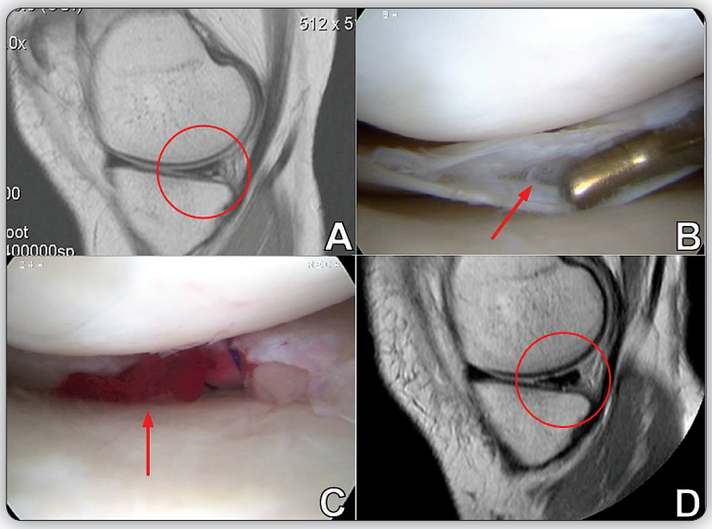

Fig. 2.
The Fish-Mouth Meniscus Tear
Fig 2A) Preoperative sagittal image documenting cleavage tear in the medial meniscus
Fig 2B) Fish mouth tear of medial meniscus with degenerative changes
Fig 2C) Intraoperative picture of collagen meniscus implant in irreparable tear
Fig 2D) Immediate postoperative sagittal MRI of collagen meniscus implant used to reconstruct fish mouth tear of the medial meniscus

led to a first of its kind rescindment of an approved 510(k).

The approval process highlights the basic difficulty in answering the following questions: Since absence of meniscus tissue has been shown to be harmful to the knee and increase the risk of developing arthritis, is regenerating tissue alone enough to justify a device approval? If it is necessary to prove meniscus tissue regeneration diminishes or prevents subsequent arthritis, then are the necessary long-term studies feasible or fundable? Additionally, do secondary measures such as improvements in pain and function in patients justify approval? Does the fact that "no harm is done if the device fails" justify a lower approval standard?

Currently, the collagen meniscus implant is approved for sale in Europe for tissue repair of the medial meniscus. The following cases are of difficult meniscus tears that currently are resected by surgeons for lack of an alternative. Post collagen meniscus implant surgery, all patients followed a carefully defined rehabilitation program (Table 1). The first three cases were conducted since FDA approval for use in the US. These cases may represent off-label use of the device. The final two cases are from the original human clinical trial with 15-year follow-ups.

1. The Fish-Mouth Meniscus Tear

A 43-year-old female injured her right knee while running. The patient complained of pain in the medial aspect of her knee and completed a series of physical therapy without relief. She presented with mild swelling, reported pain with activities at 3 on a scale of 0 – 10 with 0 being no pain, no sensation of giving way, no sensation of locking, and no difficulty descending or ascending stairs. She had pain with palpation along the medial joint line and positive Apley's, McMurray's, and hyperextension tests of the medial meniscus. MRI revealed a medial meniscus tear (Fig 2a). The patient underwent surgery 10 months after initial evaluation for medial meniscus reconstruction using a collagen meniscus

Tab. 2.
Rehabilitation Protocol Postoperative rehabilitation protocol for collagen meniscus implantation

Week	Physical Therapy	Exercises
	Maximum Protective Phase	
1	• Soft tissue treatments to musculature for edema and pain control • Passive range-of-motion exercises with flexion ≤ 90°and extension ≥ 0° • Resisted plantar and dorsi flexion at ankle. • 10 – 20% weight bearing (toe touch	• Straight leg raise exercises (supine, seated, and standing) • Non-operative, single leg stationary cycling for approximately 15 minutes per day with operative leg braced and supported • Upper extremity, core, and trunk training using light weights and bands
2-4	• Soft tissue treatments to musculature for edema and pain control • Daily manual patella glides by therapist and patient • Manual treatments to restore range-of-motion with flexion to 90 degrees • Extension range of motion should be equal bilaterally. • 10 – 20% weight bearing (toe touch) • Progression to full weight bearing initiated at 4 weeks	• Straight leg raise exercises (supine, seated, and standing) • Non-operative, single leg stationary cycling for approximately 15 minutes per day with operative leg braced and supported • Upper extremity, core, and trunk training using light weights and bands
	Moderate Protective Phase	
4-6	• Increase stretching and manual treatments to improve knee range-of-motion, with the goal of reaching full extension and flexion of 100° • Gait training to normalize movement patterns • Progressively wean off assistive devices	• Stationary cycling if tolerated • Introduction of functional exercises (partial squats, calf raises, mini step-ups, light leg pressing and proprioception exercises) • Slow walking • Home Exercise Program should be well established.
6-8	• Increase stretching and manual treatments to improve knee range-of-motion, with the goal of reaching full extension and flexion to 120° • Gait training to support normal movement patterns	• Increase intensity of functional exercises while avoiding overloading both closed- and open-chain exercises
8-12	• Range-of-motion should be near normal (0° to ≥ 120°)	• Lateral training exercises introduced (side step-ups, band-resisted side-stepping, and lateral stepping) • Begin establishment of sport specific training program
12-14	• Range-of-motion and gait should be near normal	• Increase intensity of strength and functional training for gradual return to activities • Patients are encouraged to maintain a home training program with emphasis on sport/activity specific training as well as cross training. • Low-impact activities through 16 – 24 weeks

implant, chondroplasty, and debridement. At surgery, a fish-mouth tear of the medial meniscus was found with a degenerative component within the tear(Fig 2b). The torn aspect was debrided taking care to preserve the top and bottom leaflets of the meniscus. The defect was measured and a collagen meniscus implant cut to the same size was soaked in venous blood and inserted into the defect. The implant was secured with a vertical mattress and a hay bailing suture technique (Fig 2c). The patient returned 3 days postoperatively for MRI evaluation per our IRB approved protocol for evaluating meniscus reconstructions (Fig 2d).

The fish-mouthed tear represents a dilemma for the surgeon. Resect the top leaf alone, the bottom leaf, or the whole area of the tear. Resecting the leaflets alone leaves some meniscus tissue to provide protection but being thinner, the meniscus may either re-tear or be incompentant due to its thinness. Resecting the entire area of the tear invariably leaves a large meniscus defect thereby increasing the contact forces. Repair of the fish mouth tear is fraught with difficulty as the center portion is often clearly degenerative. Sutures into the top and bottom leaflet alone leaves an abnormal shape with a poor blood supply. The use of the regeneration template in combination with needling of the periphery brings a new blood supply to the regeneration template that is now surrounded with native meniscus tissue.

2. The Degenerative Meniscus Tear with Cyst

A 48-year-old male injured his right knee while playing basketball, which led to cessation of sports. The patient reported experiencing pain and swelling with activity for a year before seeking surgical intervention. The patient presented with a stable knee and positive Apley's and McMurray's tests of the medial meniscus. MRI revealed a complex tear of the posterior medial meniscus with a degenerative cystic area in the most posterior aspect of the meniscus (Fig 3a). The patient underwent surgery one year after injury for medial meniscus reconstruction using a collagen meniscus implant, microfracture and chondroplasty to the medial femoral condyle, and debridement. At surgery, a degenerative tear into the root of the medial meniscus with an anterior fish-mouth component was found (Fig 3b). A shaver was used to debride the degenerative component. Multiple needle sticks were used to bring a new blood supply into the meniscus defect. A collagen meniscus implant was then loaded with a fibrin clot obtained from the venous blood. The blood was spun into a clot in a glass beaker with a glass rod. The defect with the collagen implant and fibrin clot (Fig 3c) was secured with a hay bailing technique using 2-0 PDS sutures. Excellent stability was obtained and bleeding was noted at the meniscus prior to closure. The patient returned 2 days postoperatively for follow-up exam and MRI (Fig 3d).

Root tears of the meniscus destroy the hoop stress absorbtion ability of the intact meniscus cartilage. When a further anterior tear is combined with a root tear the entire posterior section of the meniscus becomes incompetent. To augment healing the collagen meniscus was pre-clotted with a fibrin clot. This step improves the handling characteristics of the implant and stimulates tissue in-growth.

3. The Re-torn Bucket Handle Tear

A 26-year-old male injured his knee surfing. He had a history of meniscus repair surgery for a bucket handle tear of the lateral meniscus at age 22. The patient presented with a painful locked knee. MRI revealed a torn lateral meniscus with a degenerative component in the bucket, which was the site of the previous lateral meniscus repair (Fig 4a). Given the high rate of failure of revision meniscus repairs, especially for a bucket handle tear (Fig 4b), and given the large

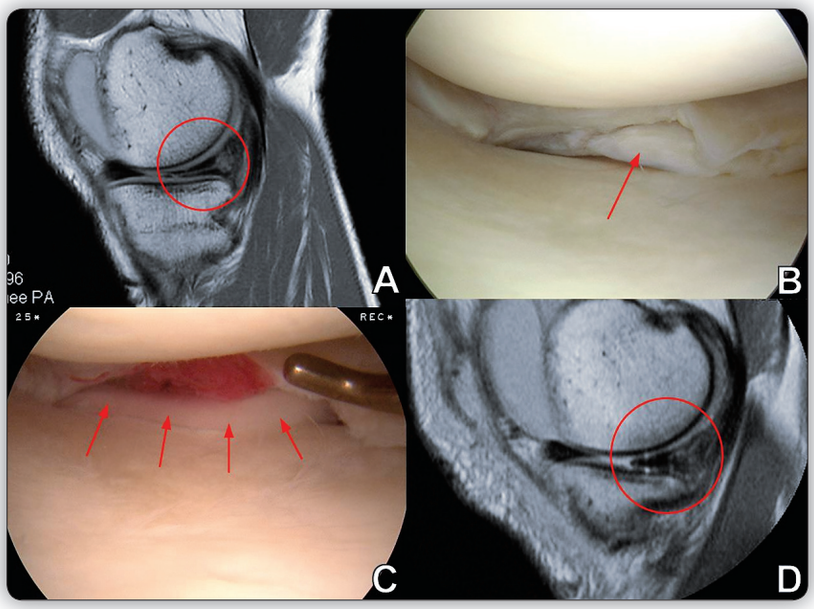

Fig. 3.
The Degenerative Meniscus Tear with Cyst
Fig 3A) Preoperative sagittal MRI documenting complete horizontal cleavage tear of the medial meniscus with round degenerative area at the posterior meniscus synovial junction
Fig 3B) Arthroscopic image of degenerative cleavage tear of the medial meniscus cartilage
Fig 3C) Collagen meniscus implant with fibrin clot inserted into cleavage tear of the meniscus
Fig 3D) Immediate post operative sagittal MRI demonstrating collagen meniscus implant sewn into place

amount of meniscus that would have to be removed if a resection alone was performed, it was elected to augment the repair with a collagen meniscus implant and fibrin clot. The patient underwent surgery 3 days later for lateral meniscus reconstruction using a collagen meniscus implant. At surgery the collagen meniscus implant was inserted into the interface between the remnant meniscus rim and the torn displaced portion of the bucket handle. The implant was augmented with a fibrin clot formed from 30 cc of venous blood stirred into a clot with a glass rod. 2-0 PDS sutures and an Athrex Meniscal Cinch suture repair (Arthrex, Inc., Naples, FL) secured the implant and the meniscus repair (Fig 4c). The patient returned 2 days postoperatively for follow-up exam and MRI (Fig 4d). The patient returned to surfing at 3 months post surgery.

Repair of a previously torn bucket handle tear of the meniscus has a very low healing rate. The meniscus edges are often rounded over. The blood supply to the displaced fragment has been lost. Resection of the displaced fragment is the most common outcome, however it leaves the patient with minimal meniscus tissue. This case demonstrates the possibility of augmenting the healing interface with the collagen scaffold and multiple needle holes to stimulate the repair process. Whether or not this will be effective over the long term is unknown, but repair without augmentation has little hope.

4. Complex Mid Section Meniscus Lesion

A 49-year-old male competed in a trail running race and noted pain and swelling with prolonged sitting, and difficulty ascending and descending stairs. The patient presented with a stable knee, pain with palpation along the medial joint line, and positive Apley's and McMurray's tests of the medial meniscus.

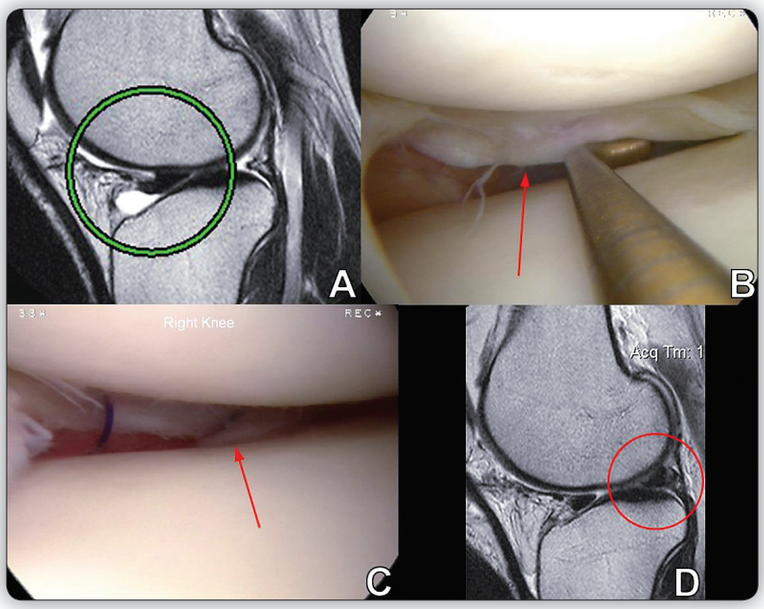

Fig. 4.
The Re-torn Bucket Handle Tear
Fig 4A) Preoperative sagittal MRI documenting bucket handle tear of the posterior horn of the lateral meniscus
Fig 4B) Degenerative inner edge of lateral meniscus displaying failed bucket handle tear repair
Fig 4C) Sandwich repair of degenerative bucket handle tear, collagen meniscus implant, fibrin clot, and native meniscus rim
Fig 4D) Immediate post operative sagittal MRI documenting collagen meniscus implant

MRI revealed a torn medial meniscus (Fig 5a). The patient underwent surgery three months after onset of pain and swelling for medial meniscus reconstruction using a collagen meniscus implant, microfracture to the trochlear groove, chondroplasty, and debridement. At surgery, a complex tear of the posterior and mid aspect of the meniscus cartilage was found (Fig 5b) in addition to an articular cartilage lesion at the trochlear groove. After shaving of the torn tissue, the defect measured 10mm by 20mm in length. A horizontal cleavage component of the tear extended into the posterior horn. A collagen meniscus implant was sewn into the defect using 2-0 PDS inside out suture technique. The small trochlear chondral lesion was microfractured. A carefully defined rehabilitation program was then initiated (Table 1), yet the patient was aggressive in his rehabilitation program, relatively non-compliant with his crutch protection during the first month, and returned to running by three months. MRI four months post collagen meniscus implantation shows regenerated medial meniscus tissue. (Fig 5c). The patient underwent arthroscopy with biopsy and histology (Fig 5e) 6.5 months later per the IRB approved protocol. The meniscus was found to be healed with 11mm wide tissue from meniscosynovial junction to the inner most margin at the site of the collagen meniscus implant (5d). The undersurface was mildly fibrillated. A 1-2 mm loose flap at the inner margin was trimmed and a biopsy obtained. Three years post collagen meniscus implant surgery, the patient was running 25 – 35 miles per week and competing in triathlons. MRI at this time revealed expected position of the native meniscus with no gross fragmentation or displacement. MRI 15 years post collagen meniscus implant surgery documented evidence of meniscus regeneration with some mild irregularity at the inner portion of the

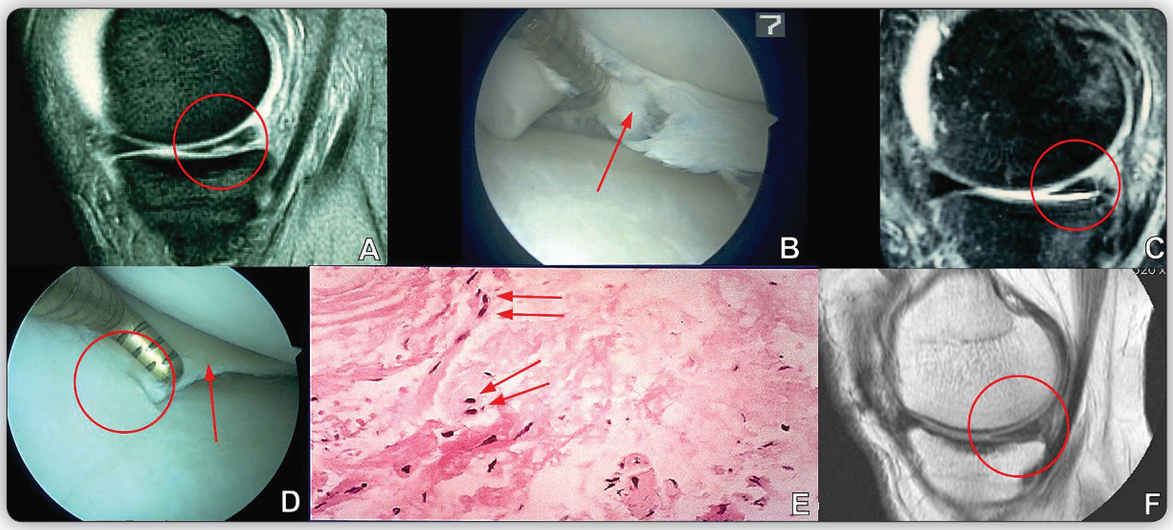

Fig. 5.
A Complex Midsection Meniscus Lesion
Fig 5A) Preoperative sagittal MRI documenting undersurface tear of medial meniscus
Fig 5B) Arthroscopic image of undersurface and degenerative tear of the medial meniscus
Fig 5C) Four month postoperative sagittal MRI demonstrating regenerated medial meniscus tissue
Fig 5D) Second Look Arthroscopy 6.5 Months Post Collagen Meniscus Implant demonstrating regenerated meniscus tissue (arrow) with small radial defect (circle).
Fig 5E) Histology of regenerated cartilage 6.5 months post collagen meniscus implant demonstrating repopulation of the collagen scaffold with host fibrochondrocytes.
Fig 5F) Sagittal MRI 15 years post collagen meniscus implant demonstrating regenerated meniscus tissue

inner portion of the meniscus at the side of the implant (Fig 5f).

Fifty-year-old patients who run and develop a meniscus tear are at a significant risk of developing degenerative arthritis. The patients are often unwilling to give up impact sports. Repair of tissues in this age group has not been highly successful. Reconstructing the meniscus defect left after meniscectomy offers the possibility of joint protection. This 15-year follow up in this active runner demonstrates the regenerated meniscus tissue and the intact joint surfaces.

5. Salvage of Failed Meniscectomy with Recurrent Complex Degenerative Tear

A 42-year-old female initially injured her knee skiing at age 10. She underwent surgery and was casted for a week at that time. She reinjured her knee at age 39 rollerblading. She underwent arthroscopy three months later for partial medial meniscectomy and removal of a loose osteochondral fragment. One week after surgery, she reinjured herself turning over in bed and withstood the pain for a year and a half before clinical evaluation. The patient presented with moderate pain, slight swelling, and difficulty ascending and descending stairs. She had pain with palpation of the medial joint line, and positive Apley's and McMurray's tests of the medial meniscus. MRI revealed a tear of the posterior horn of the medial meniscus with inferior surface extension (Fig 6a). The patient underwent surgery two years after the most recent injury for medial meniscus reconstruction using a collagen meniscus implant. Surgery revealed a large complex, degenerative tear of the medial meniscus (Fig 6b). The undersurface of the meniscus appeared to be sheared off and displaced into the joint. The tissue was debrided back to a stable base. The defect size was measu-

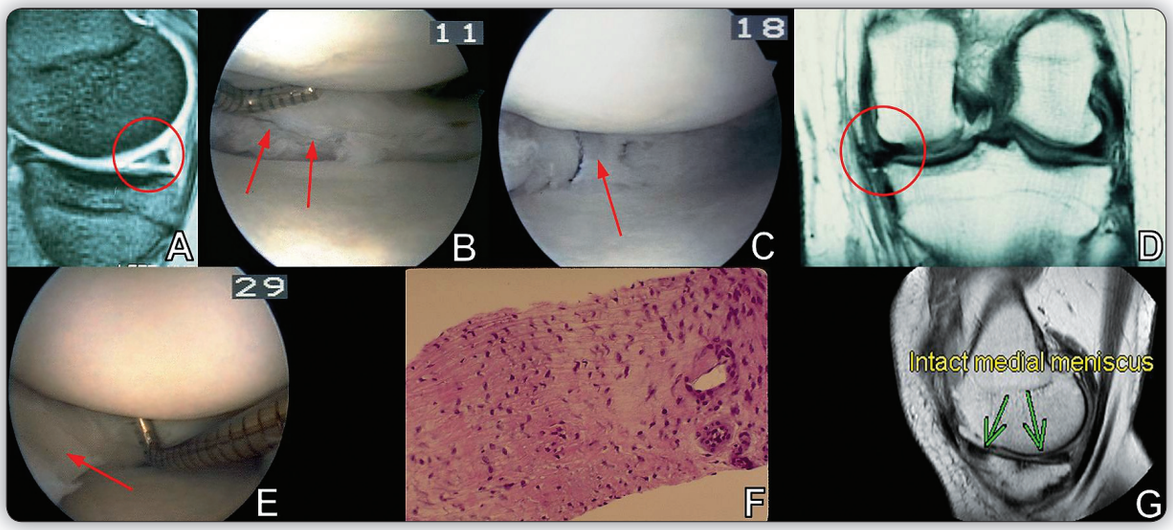

Fig. 6.
Salvage of Failed Meniscectomy with Recurrent Complex Degenerative Tear
Fig 6A) Preoperative sagittal MRI documenting degenerative tear of the medial meniscus
Fig 6B) Arthroscopic image documenting complex degenerative tear of the medial meniscus
Fig 6C) Collagen meniscus implant sutured in place
Fig 6D) Three week postoperative coronal MRI demonstrating regenerated medial meniscus tissue
Fig 6E) Second Look Arthroscopy 3 Months Post Collagen Meniscus Implant demonstrating regenerated tissue at collagen meniscus implant site
Fig 6F) Histology of regenerated cartilage 3 months post collagen meniscus implant demonstrating repopulation of the collagen scaffold with host fibrochondrocytes
Fig 6G) Sagittal MRI 15 years post collagen meniscus implant documenting intact, regenerated medial meniscus tissue

red with a calibrated probe and noted to be 24 mm in length and 6 mm in width. The collagen meniscus implant was trimmed to match. The implant was soaked in venous blood for one minute and then inserted into the meniscus defect using a pull through stitch and grasper. Inside-out 2-0 PDS suture was then used to place vertical mattress sutures securing the implant to the native meniscus tissue (Fig 6c). MRI 3 weeks post collagen meniscus implant shows regenerated medial meniscus tissue (Fig 6d). Patient underwent a second look arthroscopy with biopsy 3 months later per the IRB approved FDA protocol. The implant was in place with new healed, regenerated tissue (Fig 6e). A 2 mm defect in the radial plane was noted. A biopsy was obtained from the superior to inferior surface (Fig 6f). The patient was seen annually for 5 years then every five years thereafter with a full return to sports without pain. The patient returned for her 15-year follow up evaluation and reported no pain. MRI documented an intact medial meniscus, with a subchondral osteophyte within the medial femoral condyle and a small ganglion cyst medial to the MCL (Fig 6g).

Failed meniscectomy in forty year old women represents a high likelihood of progression to artificial joint replacement. Repeat meniscectomies increases the likelihood of early onset osteoarthritis. Meniscus reconstruction lead to both pain relief and joint preservation over 15 years.

Conclusion

Each of the patients included in this article presented with irreparable meniscus tears and underwent meniscus reconstruction with a collagen meniscus implant. Meniscectomy alone would have left them with

significant loss of tissue in the area deemed most important for force absorption and joint protection, the posterior third of the meniscus cartilage. While we cannot prove that restoration of this tissue will prevent secondary traumatic arthritis, the ability to restore the tissue gives us hope that future diagnostic tools will document the joint preservation. The collagen meniscus implant serves as a regeneration template for tissue repair. It is an ideal clot carrier and may be developed in the future for carrying specific cell factors, stem cells and anabolic agents. Currently, it is available for use in Europe in the knee joint for tissue repair and may extend the range of repairable meniscus lesions. In our hands, reconstruction of missing meniscus tissue and treatment of complex, degenerative tears is possible by the use of the collagen meniscus implant.

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