New on the Horizon: Meniscus Reconstruction Using Menaflex™, a Novel Collagen Meniscus Implant

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Contents

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The Menaflex™ Collagen Meniscus Implant

Introduction and Rationale

Tissue engineering is a relatively new discipline that has recently received significant attention [14]. Tissue engineering provides a fundamental understanding and technology that has permitted the development of structures derived from biological tissues. Bioresorbable collagen matrices are important examples of innovative new devices that resulted from the discipline of tissue engineering [2–4]. These collagen matrix materials have many positive features for use in preservation and restoration of meniscus tissue, including a controlled rate of resorption based on the degree of cross-linking. Most noteworthy, processing of the collagen can minimize any immune response, and the extremely complex biochemical composition of the normal meniscus might be recapitulated during the production process. [2–4]. If such a material could serve successfully as a scaffold for regeneration of new tissue, then many of the previously noted negative effects of losing the meniscus cartilage might be prevented or at least minimized [1].

We started development of this collagen scaffold, which we refer to as the collagen meniscus implant (CMI) and which is now marketed as "Menaflex"™, with straightforward goals. We set out to generate or grow new meniscus-like tissue in an effort to restore or preserve the critical functions of the meniscus [5, 6, 10, 11]. We also hoped to prevent further degenerative joint disease and osteoarthritis that would likely progress and lead to multiple surgeries, possibly including partial or total knee replacement. Another goal for this regenerated tissue was to enhance joint stability. And finally, we wanted the implant and the new tissue to have the effect of providing pain relief and precluding the necessity for constant medication. We also focused on several criteria for design of the collagen meniscus implant [5, 6, 10, 11]. We wanted a material that would be resorbable over time so that as the collagen of the scaffold was metabolized, the regenerated tissue would have the opportunity to replace it. We also planned for the collagen meniscus implant to maintain its

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structural integrity in the intraarticular environment for a period that would be adequate to support the new matrix formation and maturation. It was essential that the material be non-immunogenic to minimize reactions that might cause rejection or destruction of the implant. Consequently, biochemical techniques were developed as part of the processing procedures to minimize such reactions [2–4]. We designed the implant to be technically straightforward to implant surgically with a minimum of sizing considerations. We felt that the implant would have to be non-abrasive, not produce any wear particles, and not incite an excessive inflammatory response. And finally, it was extremely critical that the implant be non-toxic to the cells that invaded the scaffold and eventually produced the new matrix [5, 6, 10, 11].

Hence, it was our hypothesis that if we could provide such an environment, the meniscus fibrochondrocytes, or other progenitor cells as we would learn later, would migrate into the scaffold, divide and populate the scaffold, produce extracellular matrix, and finally lead to the generation of new meniscus-like tissue. This new tissue then would preserve and help restore the damaged meniscus cartilage and would function like the meniscus to be chondroprotective. We affirmed our hypothesis and confirmed that we had met our requirements in various animal studies [4, 5, 10, 12].

CMI Fabrication

The Menaflex CMI (Fig. 1) is fabricated from bovine Achilles tendons. The tendon tissue is trimmed and minced and then washed copiously with tap water to remove blood residue and water soluble materials. The Type I collagen fibers are purified using various chemical treatments such as acid, base, and enzymatic processes to remove non-collagenous materials and lipids. The isolated Type I collagen fibers then are analyzed for purity. After further processing, terminal sterilization is done by gamma irradiation [2–4].

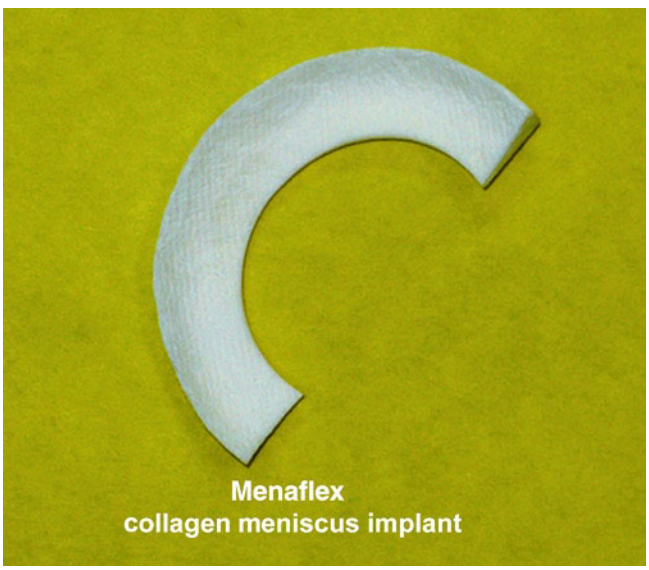

Fig. 1 The Menaflex collagen meniscus implant as it appears prior to implantation

Indications

Initially, the Menaflex was designed only for use in the medial compartment of the knee. However, a lateral Menaflex has been developed and is in use outside the United States. The Menaflex is indicated for use in acute or chronic irreparable meniscus injuries or after previous partial meniscectomy [8]. There must be enough remaining meniscus rim to which the implant can be sutured. The Menaflex is contraindicated after total meniscectomy, if there is uncorrected ligamentous instability, if there is uncorrected axial malalignment, if there is untreated full-thickness loss of articular cartilage with exposed bone, or if there is documented evidence of allergy to collagen [8]. Other systemic conditions may also preclude use of the implant.

Surgical Technique

The Menaflex is placed using arthroscopic surgical procedures [7–9, 13]. The damaged meniscus tissue is debrided minimally until healthy tissue is reached. If the debridement does not reach the red-red zone of the meniscus, a microfracture awl or similar instrument is used to perforate the host meniscus rim until a bleeding bed is assured [7–9]. A special malleable measuring device developed for this procedure is used to measure the exact size of the defect. The collagen meniscus implant is measured and trimmed to the correct size on the sterile field of the operating environment to fit the meniscus defect. If an inside-out suture technique is to be used, a posteromedial or posterolateral incision is made approximately 3 cm in length parallel and just posterior to the collateral ligament directly over the joint line so that the inside-out meniscus repair needles can be captured and the sutures tied over the capsule [7–9]. A specially designed introducer which protects the rehydrated implant is inserted through the ipsilateral portal, and then a plunger pushes the implant out of the delivery device and into the joint. Alternatively, the Menaflex can be inserted into the joint dry with the aid of an atraumatic vascular clamp.

After satisfactory positioning, the implant is sutured to the host meniscus rim using standard inside-out techniques with zone specific meniscus repair cannulae [7–9]. We prefer

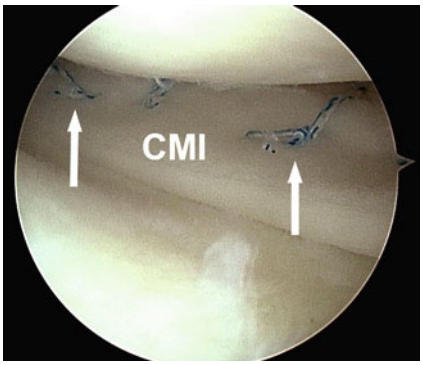

Fig. 2 The Menaflex (CMI) has been inserted into the lesion and is being sutured into place using an all-inside technique (*arrows*)

to use a suture "gun", called the SharpShooter® (ReGen Biologics, Hackensack, New Jersey), to pass the sutures. Sutures are placed approximately 4–5 mm apart using size 2-0 nonabsorbable braided polyester suture material. Sutures are placed in a vertical mattress pattern around the rim of the meniscus remnant, and a horizontal pattern is used in the anterior and posterior horns [7–9]. Typically, six to eight sutures are used to secure the implant in place. The sutures then are tied over the capsule in a standard manner. Recently, we have gained positive experience with use of an all-inside fixation technique (Fig. 2). For the all-inside technique, we prefer the FasT-Fix® (Smith & Nephew, Andover, MA). However, additional care must be exercised to avoid damage to the implant when using all-inside devices because they usually are larger and stiffer than the SharpShooter needles and sutures.

Clinical Studies

In a Phase II feasibility study, eight patients underwent arthroscopic placement of the collagen meniscus implant to reconstruct and restore the irreparably damaged medial meniscus of one knee during the first half of 1996 [7]. Seven patients had one or more prior partial medial meniscectomies, and one patient had an acute irreparable medial meniscus injury. Patients were observed with frequent clinical, serological, radiographic, and magnetic resonance imaging (MRI) examinations for at least 24 months (range, 24–32 months) initially. As a part of the initial study, all patients underwent relook arthroscopy and biopsy of the CMI-regenerated tissue at either 6 or 12 months after implantation [7]. All patients improved clinically from preoperatively to 1 and 2 years postoperatively based on pain, Lysholm scores, Tegner activity scale, and self assessment. Relook arthroscopy revealed tissue regeneration in all patients with apparent preservation of the joint surfaces based on visual observations. Based on measurements, the average amount of meniscus loss (defect) before placement of the Menaflex was 62%. That is, only 38% of the meniscus remained. At the initial relook surgery, the average filling of the meniscus defect was 77% with a range of 40–100% based on actual measurements. Histological analysis of the CMI-regenerated tissue confirmed new fibrocartilage matrix formation. Radiographs confirmed no progression of degenerative joint disease in the medial compartment [7].

As a part of a long term (5–6 years) follow-up study, all eight patients described above returned for clinical, radiographic and MRI examinations [9]. Clinical outcomes measurements were virtually unchanged from the 2-year follow-up examination. Radiographs confirmed that the medial compartment chondral surfaces continued to be protected from further degeneration. MRI revealed that the CMI-regenerated tissue continued to mature, and it was often indistinguishable from the native meniscus tissue. All eight patients underwent relook arthroscopy to assess the status of the CMI-regenerated tissues as well as the condition of the chondral surfaces. The CMI-regenerated tissue appeared similar to the earlier relook arthroscopy, and its appearance was meniscus-like, both grossly and histologically [9].

At arthroscopy the amount of the original meniscus defect remaining filled by newly generated meniscus-like tissue was determined with physical measurements and by comparison to video images of the index surgery and the first relook procedures. Physical measurements were made using the same arthroscopic measuring device that had been used during the index surgery. For example, if the original implant was 50 mm long and 7 mm wide, then it covered an area of 350 mm^2. If the newly generated tissue was measured and determined to cover 300 mm^2, then the original defect was calculated to remain 86% filled. The average amount of the original defect remaining filled at nearly 6 years after placement of the CMI was 69% with a range of 50–95% [9]. That is, only a small loss of tissue had occurred since the initial relook about 5 years earlier when 77% of the defect was filled on average [7]. By adding the amount of filled defect to the amount of meniscus remaining at the time of index surgery, this group of eight patients had 81% of their normal meniscus (range, 66–98%) at about 6 years after placement of the CMI [9]. No negative findings, such as damage to the chondral surfaces or exuberant tissue growth, attributable to the implant were observed [9].

The positive results of this Phase II feasibility study after 2 years [7] led to FDA approval of a large multicenter randomized (Menaflex versus partial meniscectomy alone) clinical trial of more than 300 patients in the United States [8]. Sixteen sites with 26 surgeon-investigators enrolled 311 patients with an irreparable medial meniscus injury or a previous partial medial meniscectomy. There were two study arms, acute and chronic. There were 157 patients with no prior surgery to the

involved meniscus ("acute") and 154 with one to three prior meniscus surgeries ("chronic"). Patients randomly either received the Menaflex or served as partial meniscectomy only controls. Patients underwent frequent clinical follow-up examinations through 2 years and completed validated outcomes scores through 7 years. Patients receiving a collagen meniscus implant were required by protocol to have 1-year relook arthroscopy to determine the amount of new tissue growth and to obtain a biopsy to assess tissue quality. Reoperation rates and survivorship analysis were determined [8].

For patients enrolled in this multicenter study at our institution ($n=41$), no serious or unanticipated complications were attributed to the implant. Patients routinely returned to daily activities by 3 months and most were fully active by 6 months, and then they continued to improve through at least 2 years as evidenced by Tegner and Lysholm scores. ELISA testing failed to detect any increase in antibodies to the collagen material. No increased degenerative joint disease was observed, nor was there radiographic evidence of further joint space narrowing. Sequential MRI examinations revealed progressive signal intensity changes indicating ongoing tissue ingrowth, regeneration, and maturation of the new tissue. At relook arthroscopy, gross appearance and shape of the regenerated tissue generally were similar to native meniscus cartilage with solid interface to the host meniscus rim in the majority of patients. The average amount of defect filled, calculated as described above, was greater than 50% with a range of 40–90%. Histologically, the collagen implant was progressively invaded and replaced by cells similar to meniscus fibrochondrocytes with production of new matrix (Fig. 3). No inflammatory cells or histological evidence of immunologic or allergic reactions were observed.

For all patients in the multicenter trial, we prospectively determined changes in Tegner activity levels from preoperative to 2 years postoperative in patients who received the Menaflex and were documented to have >50% total meniscus tissue at 1-year relook arthroscopy [8]. One hundred thirty-eight patients 18–60 years old underwent partial medial meniscectomy and placement of a Menaflex to fill the meniscus defect. There were 64 acute (no prior meniscus surgery) and 74 chronic (one to three prior partial meniscectomies on the involved meniscus) patients in this analysis. At index surgery, meniscus defect size was measured with specially designed instruments, and the percent of meniscus loss was calculated based on these actual measurements. Relook arthroscopy was performed at 1 year on 124 patients (90% surgical follow-up), and percent total meniscus surface area coverage (remnant+new tissue) was determined by making these same measurements and calculations. Patients were followed clinically for a minimum of 2 years after implant placement. At each follow-up, all patients completed questionnaires, including a Tegner score to assess activity. We then determined changes in Tegner score from the index surgery to 2 years status post implant placement in these patients [8].

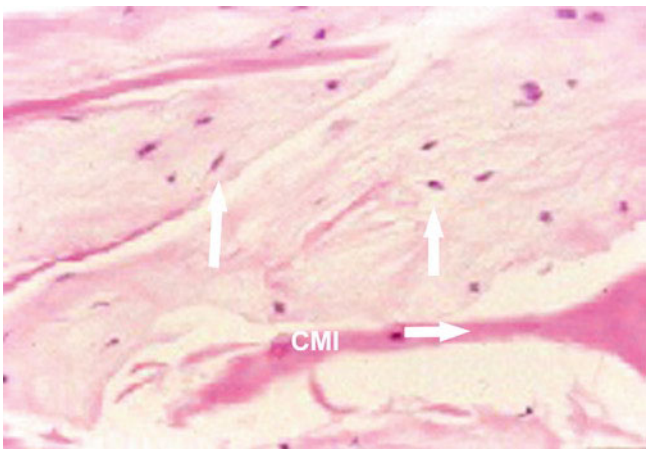

Fig. 3 The Menaflex was progressively invaded and replaced by cells similar to meniscus fibrochondrocytes (*vertical arrows*) with production of new matrix. Some implant remnants (CMI) are noted by the *horizontal arrow*. Original magnification = 100×

Of 124 relooks, 111 patients (90%) had >50% total meniscus tissue. In these patients, average Tegner activity scores improved by two levels from three to five from preoperative to 2 years status post implant. This increased change in activity levels significantly correlated with total meniscus tissue >50% ($r=0.21$, $p=0.02$). These findings mirrored those we previously reported for partial meniscectomy patients in which >50% of the meniscus was maintained. Based on these observations, we conclude that there is a significant correlation between change (increase) in Tegner activity levels over 2 years and percent total meniscus tissue in patients who receive the Menaflex as treatment for meniscus loss and have >50% total meniscus tissue. This study confirms the importance of preserving as much meniscus tissue as possible at the time of repair or meniscectomy. It clearly supports the potential positive benefits of regrowing or regenerating lost meniscus tissue to assist patients in regaining their activity [8].

In the control group of this same randomized study, we prospectively determined the amount of tissue loss at time of partial medial meniscectomy and then correlated the extent of meniscus loss with clinical symptoms, function, and activity levels 2 years following the index meniscectomy. One hundred forty-nine patients 18–60 years old underwent partial medial meniscectomy and served as controls. There were 81 acute (no prior meniscus surgery) and 68 chronic (one to three prior partial meniscectomies on the involved meniscus) patients in this analysis. At index surgery, size of the meniscus defect was measured using specially designed instruments, and percent of meniscus loss was calculated based on actual measurements. Patients were followed clinically for a minimum of 2 years following meniscectomy. At each follow-up, every patient completed questionnaires including Lysholm and Tegner scores to assess function and activity. Amount of meniscus tissue at index surgery was correlated

with the individual domains of the Lysholm scale. Tegner index was calculated to determine the amount of lost activity regained 2 years after surgical intervention [8].

Two-year data were available for 127 patients (85% follow-up). There was a significant correlation between the amount of meniscus tissue remaining following the index meniscectomy and 2-year Lysholm domains of squatting ($r=0.28$, $p=0.001$), stair-climbing ($r=0.25$, $p=0.004$), and swelling ($r=0.26$, $p=0.003$). In particular, it is noteworthy that patients who had >50% of their meniscus remaining had significantly better function than patients who had <50% meniscus remaining. Patients who had worse or no improvement in pain symptoms at 2 years averaged 42% meniscus remaining, while patients who had improved pain scores had on average 51% meniscus remaining. Tegner index for patients with <50% meniscus remaining averaged 24%, and for patients with >50% meniscus remaining averaged 52% ($p=0.02$); hence, a greater amount of meniscus tissue remaining allowed patients to regain significantly more of their lost activity. Based on these findings, we concluded that there is a significant correlation between the amount of meniscus tissue removed at meniscectomy and symptoms, function, and activity 2 years after surgery. This study confirms the importance of preserving as much meniscus tissue as possible at the time of meniscus repair or meniscectomy as well as the potential positive benefits of regrowing or replacing lost meniscus tissue in order to minimize clinical symptoms that may be suggestive of early degenerative changes.

We then carried out longer term follow-up [8]. In the acute group, 75 patients received the Menaflex and 82 were controls. In the chronic group, 85 patients received the implant and 69 were controls. Mean follow-up was 59 months (range, 16–92). Based on 141 relooks at 1 year, the Menaflex implant resulted in significantly ($p=0.001$) increased meniscus tissue compared to the original index partial meniscectomy. The implant supported meniscus-like matrix production and integration as it was assimilated and resorbed. Chronic patients receiving an implant regained significantly more of their lost activity (Tegner index) than did controls ($p=0.02$). Through 5 years, chronic patients receiving an implant underwent significantly fewer non-protocol reoperations ($p=0.04$). No differences were detected between the two treatment groups in acute patients [8].

Based upon our personal experiences with the limited long term feasibility study [9] and the randomized multicenter clinical trial [8], we conclude that the Menaflex (CMI) is implantable, biocompatible, and bioresorbable. It supports new tissue regeneration as it is resorbed, and the new tissue appears to function similar to normal meniscus tissue. While the advantage of the Menaflex, as opposed to partial meniscectomy alone, in limiting the progression of degenerative joint disease over the long term has not been definitely proven yet, the results of the studies described above provide evidence that a collagen meniscus implant-based, tissue-engineered meniscus structure can survive within the joint. Based on the relook procedures, the chondral surfaces are protected by the CMI-regenerated tissue. No serious or unanticipated complications directly related to the Menaflex have thus far been observed, and most patients have functioned well based on clinical examination and outcomes assessment. Relook arthroscopy results are positive and encouraging. These findings lend strong support to the concept that a collagen meniscus implant can be used to replace irreparable or removed meniscus tissue.

References

1. Arnoczky, S.P.: Building a meniscus. Biologic considerations. Clin. Orthop. Relat. Res. **367**, S244–S253 (1999)
2. Li, S.-T.: Biologic Biomaterials: Tissue-derived Biomaterials (Collagen). In: Bronzino, J. (ed.) The Biomedical Engineering Handbook, pp. 627–647. CRC, Boca Raton (1995)
3. Li, S.-T., Yuen, D., Li, P.C., et al.: Collagen as a biomaterial: an application in knee meniscal fibrocartilage regeneration. Mater. Res. Soc. Symp. Proc. **331**, 25–32 (1994)
4. Li, S.-T., Rodkey, W.G., Yuen, D., et al.: Type I collagen-based template for meniscus regeneration. In: Lewandrowski, K.-U., Wise, D.L., Trantolo, D.J., et al. (eds.) Tissue Engineering and Biodegradable Equivalents. Scientific and Clinical Applications, pp. 237–266. Marcel Dekker, New York (2002)
5. Rodkey, W.G.: Menaflex™ collagen meniscus implant: basic science. In: Beaufils, P., Verdonk, R. (eds.) The Meniscus, pp. 367–371. Springer, Berlin/Heidelberg (2010)
6. Rodkey, W.G., Stone, K.R., Steadman, J.R.: Prosthetic meniscal replacement. In: Finerman, G.A.M., Noyes, F.R. (eds.) Biology and Biomechanics of the Traumatized Synovial Joint: The Knee as a Model, pp. 222–231. American Academy of Orthopaedic Surgeons, Rosemont (1992)
7. Rodkey, W.G., Steadman, J.R., Li, S.-T.: A clinical study of collagen meniscus implants to restore the injured meniscus. Clin. Orthop. Relat. Res. **367S**, S281–S292 (1999)
8. Rodkey, W.G., DeHaven, K.E., Montgomery, W.H., et al.: Comparison of the Collagen Meniscus Implant to partial meniscectomy: a prospective randomized trial. J. Bone Joint Surg. Am. **90**, 1413–1426 (2008)
9. Steadman, J.R., Rodkey, W.G.: Tissue-engineered collagen meniscus implants: 5–6-year feasibility study results. Arthroscopy **21**, 515–525 (2005)
10. Stone, K.R., Rodkey, W.G., Webber, R.J., et al.: Future directions: collagen-based prosthesis for meniscal regeneration. Clin. Orthop. Relat. Res. **252**, 129–135 (1990)
11. Stone, K.R., Rodkey, W.G., Webber, R.J., et al.: Development of a prosthetic meniscal replacement. In: Mow, V.C., Arnoczky, S.P., Jackson, D.J. (eds.) Knee Meniscus: Basic and Clinical Foundation, pp. 165–173. Raven, New York (1992)
12. Stone, K.R., Rodkey, W.G., Webber, R.J., et al.: Meniscal regeneration with copolymeric collagen scaffolds: in vitro and in vivo studies evaluated clinically, histologically, biochemically. Am. J. Sports Med. **20**, 104–111 (1992)
13. Stone, K.R., Steadman, J.R., Rodkey, W.G., et al.: Regeneration of meniscal cartilage with use of a collagen scaffold: analysis of preliminary data. J Bone Joint Surg Am **79**, 1770–1777 (1997)
14. Vunjak-Novakovic, G., Goldstein, S.A.: Biomechanical principles of cartilage and bone tissue engineering. In: Mow, V.C., Huiskes, R. (eds.) Basic Orthopaedic Biomechanics and Mechano-Biology, pp. 343–407. Lippincott William & Wilkins, Philadelphia (2005)