

MENISCAL REPAIR: CURRENT STRATEGIES AND THE FUTURE OF TISSUE ENGINEERING

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INTRODUCTION

Injury to the meniscus is the most common problem of the knee joint, with an annual incidence of 60-70 per 100,000.¹⁻³ Frequently sports-related but also associated with activities of daily living, meniscal tears can result in significant physical impairment and often require surgical intervention. Operative therapies include total or subtotal meniscectomy, transplantation, or repair. While procedural choice depends on many factors, including size, location, and patient activity level, meniscectomy is the most common orthopaedic procedure performed in the United States today.⁴

Once thought to be a vestigial remnant of leg muscle, the meniscus is now recognized for its functions of tibiofemoral load transmission, shock absorption and lubrication. Since the report of Fairbank⁵ in 1948 describing radiographic changes following meniscectomy, the degenerative changes associated with total meniscectomy have been widely accepted. As a result, meniscal preservation has become the goal of therapy. Contemporary to the increasing interest in meniscal preservation have been advances in open surgical techniques as well as the development of arthroscopy. In the past two decades arthroscopic repair has gained popularity, constituting 10% to 20% of all meniscal surgical procedures.¹

In order to properly treat a patient with a meniscal tear, the clinician and researcher must be intimately familiar with meniscal anatomy and its healing potential. Briefly, the menisci are C-shaped wedges of fibrocartilage composed mostly of type I collagen fibers oriented circumferentially with a small radial

component. It is this composition that gives the meniscus its shock-absorbing and load-bearing functions. Vascularity, arguably the most important factor for healing potential, is limited to the periphery. Arnoczky and Warren⁶ characterized the blood supply to be limited to the peripheral 10% to 30% of the meniscus. Therefore, lesions located in the outer one-third have the greatest capacity for repair. In addition to location, other factors to be considered include chronicity, length, pattern, concomitant anterior cruciate ligament injury, and patient age and activity level.⁷

This article reviews current therapies as well as the advances of our laboratory in the development of a tissue engineered meniscal repair technique.

RESECTION

TOTAL MENISCECTOMY

Previously the procedure of choice, total meniscectomy is rarely performed today. Fairbank⁵ was the first to characterize the radiographic changes associated with this procedure: (1) joint space narrowing, (2) femoral condyle ridge formation over the old meniscal site, and (3) femoral condyle flattening. In addition to numerous reports corroborating these radiographic changes, the development of osteoarthritis after total meniscectomy has been confirmed in an animal model⁸ and through second-look arthroscopy. Roos et al⁹ performed a 21-year follow-up study of meniscectomized patients who suffered an isolated meniscal lesion. They reported a relative risk of 14.0 for the development of radiographic changes consistent with osteoarthritis and postulated that patients undergoing total meniscectomy may develop osteoarthritis ten to twenty years earlier than patients with primary osteoarthritis.

PARTIAL MENISCECTOMY

Due to the long-term effects of total meniscectomy, partial meniscectomy is performed when the characteristics of the lesion are not conducive to successful repair. This procedure can be performed via an open or arthroscopic technique. It may be associated with fewer postoperative complications and a reduced incidence of osteoarthritis development compared to total meniscectomy. Arthroscopy offers decreased hospitalization, shorter recovery time, and a reduction in patient care costs over open technique for this relatively common procedure.

A 15-year partial meniscectomy follow-up study by Burks et al¹⁰ reported an 88% good-to-excellent clinical outcome with minimal degenerative radiographic changes. However, Rangger et al¹¹ report considerable degenerative changes with partial removal of the meniscus. The authors describe increased

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radiographic osteoarthritic changes in 38% of medial partial meniscectomized patients and 24% of lateral partial meniscectomized patients at an average follow-up of 53.5 months. Cox and Cordell report a direct correlation between the extent of degenerative changes (pitting, erosion and fibrillation of the articular cartilage) and the amount of meniscus removed.⁸

REPAIR

Despite the trend away from meniscectomy, not all meniscal tears are suitable for repair. Commonly accepted indications for attempted repair include (1) a tear located in the peripheral 10% to 30% of the meniscus; (2) a tear within 3mm to 4mm of the meniscocapsular junction; (3) a complete vertical longitudinal tear >10 mm long; (4) a tear that can be displaced by probing; (5) a tear absent of secondary degeneration or deformity; (6) a tear in an active patient; and (7) a tear associated with concurrent ligament stabilization or in a ligamentously stable knee.^{12, 13}

Repair methods include open repair and three arthroscopic techniques: inside-out, outside-in, and all-inside. The inside-out technique involves suture placement through the meniscal tear to the outside of the joint capsule. This technique offers the advantage of consistent perpendicular suture placement through the tear, but risks neurovascular injury during suture placement outside the capsule. Therefore, an additional incision is placed posteriorly to allow retraction of neurovascular structures. Retrospective studies have reported 73% to 91% success rates based on clinical results.⁷ Tenuta and Arciero¹⁴ report an overall complete healing rate of 65% on second-look arthroscopy. In this study, the success rate was 90% when meniscal repair was performed with concomitant anterior cruciate ligament reconstruction, but was only 57% for lone meniscal repair. Meniscal repair has been widely reported to be more successful when performed with anterior cruciate ligament reconstruction (62%-96%) versus no reconstruction (17%-62%).⁷

The outside-in technique, as its name implies, involves passage of sutures from outside to inside the joint through 18-gauge spinal needles. It was developed to decrease the risk of neurovascular injury associated with the inside-out technique, and has the greatest potential for successful healing when used on tears involving the anterior and middle thirds of the meniscus.¹² Van Trommel et al¹⁵ reported complete healing in 45% of patients and partial healing in 32% of patients at an average follow-up of 15 months. The authors report no healing in patients with tears located in the posterior aspect of the medial meniscus, emphasizing the inherent difficulty of this technique to place sutures in this area.

The all-inside technique, as originally performed, is the most technically demanding, requiring special arthroscopic equipment and posterior working portals, but provides the greatest healing potential for peripheral posterior horn lesions. Recently, non-suture fixation devices, including the Meniscus Arrow (Bionx Implants, Bluebell, PA) and the T-fix Suture Bar (Smith & Nephew, Memphis, TN) have been introduced, facilitating this technique by alleviating the need for posteromedial

and posterolateral incisions required with traditional suture repair.

Advancements in arthroscopic technique have not made open repair totally obsolete. Open repair is still indicated in situations of posterior, medial meniscus tears with a tight medial compartment^{7, 16} and tears associated with multiple ligament injuries.¹² This technique is felt to offer better bed preparation and suture fixation over arthroscopy and uses the same posterior incision as the inside-out repair.

TISSUE ENGINEERING

Although there is variable success of the previously mentioned repair techniques on tears in the vascularized zone of the meniscus, there is currently no reliable treatment option that addresses tears located in the inner two-thirds of the meniscus. Tissue engineering, a discipline that combines the technologies of cell culture and biodegradable scaffolds to deliver a cellular repair, is thought to be the future answer to this problem. The concept of using cell-based repair for torn menisci could improve healing of lesions in the avascular zones and broadly expand the indication for repair rather than removal, obviating the need for meniscectomy.

In the Laboratory for Musculoskeletal Tissue Engineering at the Massachusetts General Hospital, we have demonstrated that articular chondrocytes have the potential to bond cartilage matrices together with increasing integrity over time.^{17,18} Our initial experiments involved a chondrocyte seeded scaffold placed between two devitalized cartilage plugs. After *in vivo* culture in nude mice, the samples were biomechanically analyzed by applying tensile displacements to the constructs.¹⁹ Results showed that mechanical properties (tensile strength, fracture strain, fracture energy, and tensile modulus) increased significantly with time and were three or more times greater than the unseeded experimental group (Fig. 1).

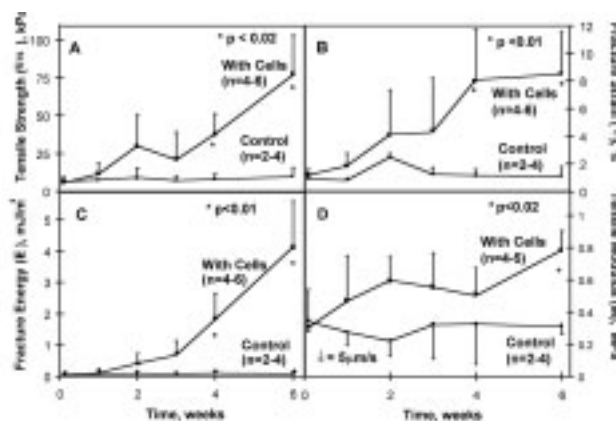


Figure 1. Time course of changes in tensile strength (A), fracture strain (B), fracture energy (C) and tensile modulus (D) over six weeks *in vivo* for constructs seeded with chondrocytes or unseeded controls. In each figure * denotes the appropriate p value for significance of difference between the experimental group and the control at that time point.

We performed a subsequent *in vivo* study to assess the ability of chondrocyte-seeded devitalized meniscal chips to repair a bucket-handle lesion placed into meniscal tissue.²⁰ The menisci were implanted into the backs of nude mice and allowed to

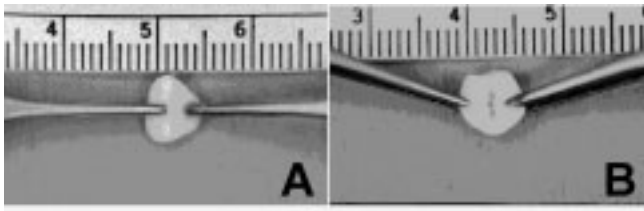


Figure 2. Macroscopic analysis of an experimental sample (A) and control sample, treated with the only suture (B) upon retrieval from nude mice. The experimental sample shows good repair, with the pre-seeded chip in the middle of the bucket-handle lesion. No separation of the fracture edges is evident with gentle traction by the two forceps. In contrast, the control sample demonstrates no attempt at repair.

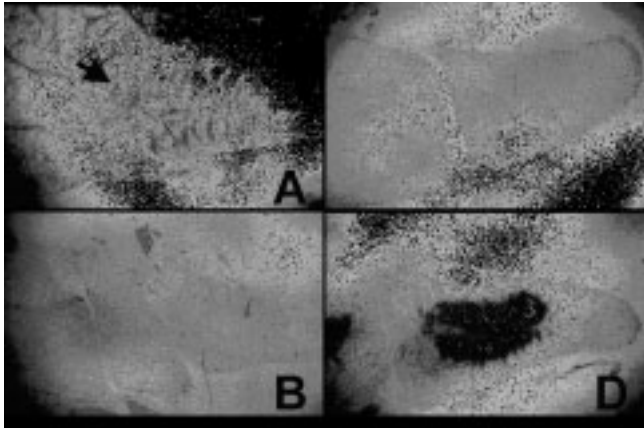


Figure 3. Photomicrographs of experimental specimen A and control specimens B, C and D (Toluidine blue, original magnification 20 X). In experimental samples (A), the meniscal chip is located in the middle of the bucket-handle lesion (arrow) allowing bonding of the two edges of the incision through the newly formed tissue, synthesized by the viable chondrocytes. In control samples (B), treated with an unseeded meniscal chip, the implant is still recognizable in the lesion (arrows) unattached to the meniscal block on either side of the incision. Analysis of the samples treated with suture-only (group C) or no suture (group D) showed no repair of the incision.

heal over 12 weeks. Initial repair tests were performed manually by pulling apart the two edges of the meniscus with two Adson forceps (Fig 2). These tests showed complete fusion of lesion margins in all experimental samples. The two edges of the bucket-handle lesion were firmly attached to the meniscal chips (still visible in between), and no separation of the lesion was noted by pulling them apart. In all control samples, repair did not occur and the lesion was still visible by distracting the edges. Histological evidence was consistent with gross findings showing a bond between edges of the lesion and the implant (Fig. 3). These results demonstrated that cell-based therapy could be a useful adjunct to meniscal repair techniques.

These studies on meniscal healing using articular cartilage chondrocytes as the cell source and devitalized meniscal chips as structural support for the chondrocytes provided the basis for a large animal preclinical model. This experiment (submitted for publication, *American Journal of Sports Medicine*) was to determine if a lesion in the avascular portion of the meniscus could be repaired *in situ* using isolated autologous cells seeded onto a scaffold. To test this hypothesis, a bucket-handle lesion was made in the medial meniscus of the left knee of sixteen Yorkshire pigs. In four animals in group A, the lesion was treated with a scaffold seeded with articular chondrocytes and

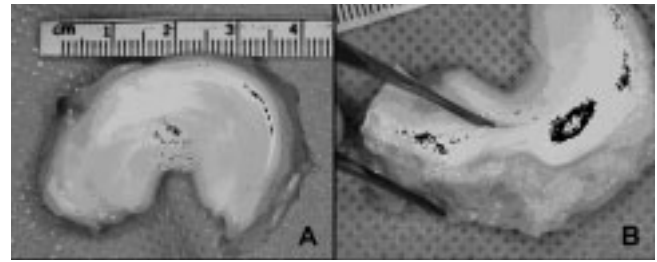


Figure 4. Macroscopic analysis of samples upon harvest. The experimental meniscus sample of group A shows healing with the pre-seeded meniscal slice still present in the middle of the bucket-handle lesion (A). On the other hand, no control samples reveal any healing of the meniscal lesion as shown in this picture from group C, where the lesion was treated with the only suture. The bucket-handle lesion is not healed and still visible (B).

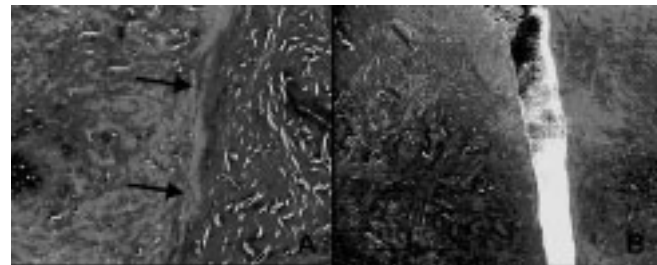


Figure 5. Histological analysis (Hematoxylin and Eosin, original magnification 100X) of a specimen of the experimental group, treated with the seeded meniscal scaffold (A) and a control sample from a meniscus treated with the suture-only (B). Whereas good healing was noted in the experimental samples (A), with good integration (arrows) between the seeded scaffold (left) and the native meniscus (right), no repair was achieved in the control specimen (B).

secured into the lesion with a suture. The scaffold material was a devitalized allogeneic meniscal cartilage. In four animals in control group B, the lesion was treated with the scaffold without seeded cells and secured with a suture. Four animals in control group C had the lesion treated with only a simple suture. The lesion was left untreated in four animals in control group D. All animals were sacrificed after nine weeks. The lesions were evaluated grossly and histologically.

Gross evaluation showed bonding of lesion margins in three out of four specimens from group A (Fig. 4A). Macroscopic analysis of all control specimens indicated no evidence of repair (Fig. 4B). Histological analysis showed complete adherence between the margins of the meniscal lesion and the cell-seeded scaffold in several areas of group A menisci (Fig. 5A); the arrows in the picture represent the limit between the scaffold (left) and the outer part of the meniscus. On the other hand, no matrix formation or signs of repair were seen in the specimens of all control groups (Fig. 5B). Histologic analysis showed complete adherence between the margins of the meniscal lesion and the cell-seeded scaffold in several areas of the menisci. Other areas of the same specimens showed interruption of continuity between the seeded scaffold and the native meniscal lesion edges. Where repair was achieved, newly formed cartilage matrix was involved in the bonding process.

Although successful, articular cartilage harvest for a clinical repair may not be optimal because of the associated donor site morbidity. Preliminary data on seeking alternate cells that

could be used to repair meniscal lesions have been generated in our nude mouse model. Two potential sources of chondrogenic cells are auricular and costal chondrocytes, as well as stem cells. We are currently testing these cell types, both autologous and allogeneic, using our previous data as a comparison. These alternative cells sources would obviate the need for harvesting articular cartilage and eliminate associated joint morbidity. It is possible that the avascular nature of the knee will permit the use of allogeneic cells as the chondrocytes will ultimately encapsulate themselves in an immune protective layer of new cartilage matrix.

SUMMARY

Current repair techniques are capable of providing successful treatment in a subset of meniscal lesions. We have demonstrated the potential of articular chondrocytes to repair tears in the avascular zone of the meniscus in a large animal model. Further studies are planned to test alternative cell sources and scaffold material.

Although a relatively new application, tissue engineering will undoubtedly be involved in the future of meniscal repair due to its potential to provide a cell-based repair applicable to all lesions, regardless of location. Conceivably, tissue engineering has the potential to offer meniscal replacement using these same principles.

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