Current Concepts

Current Trends in Anterior Cruciate Ligament Reconstruction

Part 1: Biology and Biomechanics of Reconstruction

Freddie H. Fu,* MD, Craig H. Bennett, MD, Christian Lattermann, MD, and C. Benjamin Ma, MD

From the Department of Orthopaedics, University of Pittsburgh, Pittsburgh, Pennsylvania

ABSTRACT

With today’s increasing emphasis on sporting activities, the incidence of anterior cruciate ligament injuries has also increased. Epidemiologic studies estimate that the prevalence of anterior cruciate ligament injuries is about 1 per 3000 Americans. Management of these injuries has evolved from nonoperative treatment to extracapsular augmentation and primary ligament repair to anterior cruciate ligament reconstruction. Treatment of these injuries has significantly improved over the last few decades with the application of knowledge gained from both basic science and clinical research. This article is composed of two parts. The first part reviews the biology and biomechanics of the injured anterior cruciate ligament and the basic science of reconstruction. In the second part, to be published later, current operative concepts of reconstruction, as well as clinical correlations, are reviewed. Summarizing the latest information on basic scientific as well as clinical studies regarding the anterior cruciate ligament, this article intends to demonstrate the correlation between the application of basic science knowledge and improvement of clinical outcomes.

Biomechanical analysis is recognized as a firm entity in knee ligament research. The biology of ligament healing has received a tremendous amount of interest over the past few decades with advances in knowledge of molecular biology. In this first part of the article, the biology of the injured ACL as well as pertinent and recent biomechanical and biologic studies involving the reconstructed ACL are reviewed. A goal of this section is to demonstrate the relationship between the biomechanics and the biology of ACL reconstructions.

BIOLOGY OF THE INJURED ACL

Clinical results of nonoperative treatment of the ruptured ACL have shown that the majority of these injuries lead to functionally unacceptable outcomes.25,60,61,79 Patients often complain of persistent joint instability and knee pain after such treatment. Moreover, other structures within the joint are at risk of injury in the ACL-deficient knee.74 Both biomechanical and clinical studies have found that patients with chronic ACL deficiency have an increased incidence of meniscal injuries.51,101,106 Unlike the intraarticular ACL, extraarticular ligaments such as the medial collateral ligament (MCL) have good healing potential and can have functional recovery with conservative treatment.10 The difference in healing potential has led clinicians and scientists to believe that intraarticular and extraarticular ligaments have distinctly different biologic properties.

Injuries to ligaments usually lead to the formation of local hematoma. In extraarticular ligaments, the hematoma is organized into a fibrinogen mesh where invading cells such as macrophages, monocytes, and other inflammatory cells can settle. These inflammatory cells secrete a multitude of cytokines and growth factors that can mediate inflammation and attract fibroblasts and stem cells to the injured ligament. The inflammatory response fades after a short period of time and granulation tissue is formed. The fibroblastic cells then gradually reorganize this granulation tissue to form a scar or fibrous tissue.
Unlike the MCL, the ACL is not embedded in a strong, soft tissue envelope. The ACL has a thin, vascularized envelope formed by the synovial lining. The synovial lining of the knee joint is a highly organized tissue with the capacity to expand inside the joint. When this synovial sheath is torn during injury, blood dissipates within the joint and does not form a local fibrinous mesh at the site of injury.

The dependence of ACL healing on an intact synovial lining has been demonstrated by the poor healing response in ACL transection studies performed in animals. When the synovial lining is intact, the hematoma can be kept in place, provide an organized fibrin meshwork, and promote an early inflammatory response with the associated release of cytokines and growth factors. Besides containing the blood clot, the synovium can also initiate scar formation in partial ACL ruptures. Recent research demonstrates that fibroblasts within the synovial lining can migrate toward the site of ligament injury. For complete ruptures, however, there is no local healing response detectable at the injury site. Recent clinical work suggests that surgical formation of a blood clot at the femoral insertion of the ACL after proximal, partial ACL ruptures can lead to reattachment of the ACL at its origin (J. R. Steadman, unpublished data, 1998). Once the blood clot has been able to form at the site of injury, there seems to be a potent reparative response initiated by cells within the synovial lining. Therefore, the healing capacity of complete ACL ruptures may depend on the extent of injury to the synovial sheath.

Besides loss of synovial sheath integrity, there are also changes in the intraarticular cytokine profile after ACL injury. In chronic ACL-deficient knees, the levels of proinflammatory cytokines such as interleukin-1 and tumor necrosis factor-alpha are markedly elevated; whereas protective, antiinflammatory proteins such as the interleukin receptor antagonist protein are significantly decreased. This change in cytokine profile can lead to a potentially aggressive environment, which may interfere with the regular healing response.

The differences in healing potential between intraarticular and extraarticular ligaments are not completely understood. Recent in vitro studies have shown that there are distinct differences between the intrinsic properties of ACL and MCL fibroblasts. For example, the production of extracellular matrix and collagenous proteins is significantly higher for fibroblasts within the ACL. Proliferation and migration of cells in the ACL, however, is slower than that in the MCL. Furthermore, under inflammatory conditions fibroblasts in the ACL have lower mobility than those in the MCL. Further in vivo and in vitro studies are needed to fully characterize the complicated healing process of these ligaments.

BIOMECHANICS AND BIOLOGY OF ACL RECONSTRUCTION

The poor healing capacity of the ACL observed clinically and confirmed in multiple in vitro and in vivo experiments has led orthopaedic surgeons to perform ACL reconstructions rather than repairs. In this section, we will address a few important biomechanical and biologic issues that are important for ACL reconstructions.

ACL Anatomy and Strength

The ACL is a two-bundle ligament consisting of anteromedial and posterolateral bundles that originate from the lateral femoral condyle within the intercondylar notch. The ACL inserts on the tibial plateau, medial to the insertion of the anterior horn of the lateral meniscus. Recent studies performed on young human cadaveric knees have shown the ultimate tensile load and stiffness of the human femur-ACL-tibia complex to be 2160 ± 157 N and 242 ± 28 N/mm, respectively. This intraarticular ligament is the primary restraint to anterior tibial translation. An understanding of the structural properties of the intact ACL is important, as replacement grafts should have similar tensile and dimensional properties as those of the intact ACL to best reproduce its in vivo function.

Graft Material

Because of the unfavorable results of prosthetic ligament replacements, the most popular and successful surgical replacements for the ACL have been biologic tissue grafts because of their potential for graft remodeling and integration into the joint. Biologic tissue grafts are available either as autografts or allografts. The advantages of autograft include low risk of adverse inflammatory reaction and virtually no risk of disease transmission. Allograft use, however, avoids donor site morbidity, decreases surgical time, and diminishes postoperative pain.

Autografts. Throughout the history of ACL reconstruction, various autograft choices have been used. The most common current graft choices are the bone-patellar tendon-bone graft and quadruple semitendinosus/gracilis tendon graft. The bone-patellar tendon-bone graft is usually an 8- to 11-mm wide graft taken from the central third of the patellar tendon with its adjacent patellar and tibial bone blocks. The bone-patellar tendon-bone graft has been a popular ACL replacement graft because of its high ultimate tensile load (approximately 2300 N), its stiffness (approximately 620 N/mm), and the possibility for rigid fixation with its attached bony ends.

In recent years, attention has shifted to the increased use of the hamstring tendon graft with its relatively low donor site morbidity. Hamstring tendon graft use has evolved from a single-strand semitendinosus tendon graft to a quadruple-strand semitendinosus/gracilis tendon graft, where both the semitendinosus and gracilis tendons are folded in half and combined. The dimension of a round, 10-mm quadruple semitendinosus/gracilis tendon graft is more comparable with that of the intact ACL, and its ultimate tensile load has been reported to be as high as 4108 N. The quadruple semitendinosus/gracilis tendon graft also provides a multiple-bundle replacement graft that may better approximate the function of the two-bundle ACL. Disadvantages of this soft tissue graft...
include the concern over tendon healing within the osseous tunnels and the lack of rigid bony fixation.

The quadriceps tendon graft for ACL reconstruction has also gained recent attention.\textsuperscript{30,47,62,88,110} Biomechanical studies have shown the ultimate tensile load of this graft to be as high as 2352 N.\textsuperscript{88} This replacement graft has been found to have adequate tensile properties, as well as size, for ACL reconstruction. The quadriceps tendon graft has become an alternative replacement graft, especially for revision ACL surgeries\textsuperscript{110} and for knees with multiple ligament injuries. Table 1 shows a comparison of the ultimate tensile loads of the various autografts used in ACL reconstruction.

**Allografts.** Allografts are soft tissue grafts harvested from human donors. The morbidity associated with autograft harvest and the supply of allografts have increased the interest in allografts. However, the decrease in tensile properties with sterilization and preservation as well as risk of inflammatory reaction has been a concern. Allografts are now commonly used for multiple ligament reconstructions, revision ligament reconstructions, and for patients who are not high-performance athletes.

Commonly available allografts for ACL reconstruction include the patellar tendon and Achilles tendon. With their immunogenic potential and risk of disease transmission, allografts need adequate preparation before implantation. The effects of preservation and sterilization on the biomechanical properties of the allograft have been thoroughly studied. Allografts are usually preserved by deep freezing or freeze-drying. Deep freezing without drying has little or no effect on the mechanical properties of ligaments,\textsuperscript{32,115} with no significant differences in the stiffness, ultimate load, or modulus noted between treated and control ligaments. However, freeze-thaw treatments can damage cells and matrices, resulting in inferior biomechanical properties.\textsuperscript{63}

Sterile procurement of allograft tissues is optimal to avoid contamination; however, this process can be both expensive and time-consuming. Secondary sterilization can be achieved by ethylene oxide or gamma irradiation, but each has detrimental effects on the allograft. Ethylene oxide derivatives remain on the tissue after ethylene oxide sterilization, despite extensive aeration techniques. These remains, namely ethylene glycol residues, can be retrieved at surgery in reconstructed knees.\textsuperscript{56} Currently, this method is not recommended for allograft sterilization. Gamma irradiation can reduce the risk of disease transmission; however, it also has adverse effects on the tensile properties of ligaments. A trend toward decreased structural and mechanical properties of the tissue has been observed with irradiation, with a significant decrease seen at the 3-Mrad level of dosage.\textsuperscript{34,36,103} Irradiation also alters tissue morphology, during which collagen fascicles become separated and the ligaments become visibly crimped. To date, allografts are usually harvested in a sterile environment and kept sterile by deep freezing, or low-dose irradiation is used to achieve sterilization.

Besides differences in structural properties, the biologic properties of allografts are also different from those of autografts. In an animal study comparing goat patellar tendon allograft and autograft, the knees that were reconstructed with autografts had smaller increases in anteroposterior laxity, higher ultimate tensile load, and more advanced biologic incorporation when compared with allograft-reconstructed knees.\textsuperscript{54} This study indicated that allografts have slower incorporation than autografts at 6 months after surgery. Both animal and clinical data suggest that, as with autograft tissue, allograft tissue revascularizes and becomes viable after implantation.\textsuperscript{9,54,98,99}

There are a few studies demonstrating that the rate of graft incorporation and remodeling are slower for allograft than autograft reconstructions.\textsuperscript{28,54} In addition, there are some animal studies demonstrating a deterioration of allograft tissues after implantation.\textsuperscript{24,54,99} However, clinical studies have demonstrated minimal differences between allograft and autograft reconstruction at 3 to 5 years of follow-up.\textsuperscript{39,97}

**Graft Placement**

An important aspect in ACL reconstruction is the placement of the soft tissue graft. Significant research has been devoted to identifying the ideal position for graft placement with the hope of being able to best reproduce the anatomy and function of the intact ACL. The cross-sectional area of the intact ACL changes between its midsubstance and at the insertion sites, where the ligament broadly inserts over the lateral intercondylar notch proximally and over the anterior tibial plateau distally.\textsuperscript{40} Because there are broad insertion sites, a number of locations for graft placement have been evaluated in an attempt to obtain the best replication of the in vivo function of the ACL. Isometric placement of the ACL replacement graft was favored over other methods in the past.\textsuperscript{42,43} Isometric graft placement limits changes in graft length and tension during knee flexion and extension. This concept was initially introduced to avoid significant changes in graft tension during flexion and extension, which may possibly lead to overstretching or failure of the graft. However, the concept of isometry is now considered oversimplified, as recent basic science studies have shown that the normal ACL is not isometric. The fiber bundles of the ACL are under variable stress during knee motion. For example, the anteromedial bundle of the ACL experiences higher stress during flexion, and the posterolateral bundle experiences higher stress during extension.\textsuperscript{31}

### Table 1

<table>
<thead>
<tr>
<th>Graft type</th>
<th>Ultimate tensile load (N)</th>
</tr>
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<tbody>
<tr>
<td>Intact ACL</td>
<td>2160 ± 157\textsuperscript{14}</td>
</tr>
<tr>
<td>Bone-patellar tendon-bone (10 mm)</td>
<td>2376 ± 151\textsuperscript{88}</td>
</tr>
<tr>
<td>Single-strand semitendinosus</td>
<td>1216 ± 50\textsuperscript{88}</td>
</tr>
<tr>
<td>Quadruple hamstring graft</td>
<td>4108 ± 200\textsuperscript{16}</td>
</tr>
<tr>
<td>Quadriceps tendon (10 mm)</td>
<td>2352 ± 495\textsuperscript{88}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Measurements in parentheses are widths of the graft. Reference numbers refer to studies revealing higher limits of the ultimate tensile load.
With the use of robotic technology, the in situ force in the ACL has been identified in response to an anterior tibial load. The in situ force in the ligament is defined as the force carried by the ligament in its natural environment. The in situ force in the ACL in response to an anterior tibial load is highest at 30° of knee flexion and slowly decreases with increasing knee flexion. The in situ force in the posterolateral bundle shows a similar trend as the intact ACL, while the in situ force in the anteromedial bundle remains relatively unchanged throughout the range of knee flexion and extension (Fig. 1).85,86

Graft placement in ACL reconstructions has changed with advances in understanding the importance of each bundle of the ACL. A number of investigators advocate graft placement at the posterior portion of the ACL tibial insertion site, near the posterolateral bundle position, for best reproduction of the function of the intact ACL.5,48,50 Besides best reproducing the in situ force, this placement decreases graft impingement with knee extension (Fig. 2). An anteriorly placed tibial tunnel can limit knee extension when the graft impinges on the roof of the intercondylar notch. While it is now generally accepted that placement of the tibial tunnel should be at the central or posterior portion of the tibial insertion site of the intact ACL tibial insertion, the ideal position for graft placement is still unknown.

Initial Graft Tension

Besides graft placement, the tension applied to the replacement graft at the time of graft fixation, or initial graft tension, can significantly alter joint kinematics and in situ forces in the graft during knee motion. A low initial graft tension will not provide joint stability. An exceedingly high initial graft tension can restrain joint motion and compromise graft survivability. Clinically, many investigators have suggested an initial tension near 44 N, or 10 pounds, but this tension is empirically chosen and is not scientifically based.

The effect of initial graft tension was first studied in a canine ACL reconstruction study.118 Initial graft tension of 1 versus 39 N on patellar tendon autografts was examined. At 3 months, no differences were found in anteroposterior joint stability or in tensile properties of the bone-graft-bone complex. However, the reconstructed knees that had an initial graft tension of 39 N did demonstrate some histologic evidence of degeneration of the articular cartilage. The effect of initial graft tensioning was also examined in a prospective, randomized study of human ACL reconstructions.117 In this study, patients were randomly divided into three groups based on initial graft tension of 20, 40, and 80 N. At a minimum 2-year follow-up, the group with an initial graft tension of 80 N had significantly less anterior laxity than the group with an initial graft tension of 20 N. There were no reported differences in clinical symptoms for the three groups. However, this study is a short-term follow-up report, and long-term effects of initial graft tension on the outcome of ACL reconstruction remains a subject to be investigated.107,117

As mentioned earlier, the in situ forces in the ACL change with flexion and extension. A recent cadaveric study compared the kinematics of the ACL-reconstructed knee with the graft tensioned and fixed at full extension and at 30° of knee flexion.113 In response to a simulated anterior drawer test, the anterior translation was significantly less in the latter group (Fig. 3). This study demonstrated that the flexion angle of the knee at the time of graft fixation can significantly affect the resulting kinematics of the reconstructed knee and should be considered when performing ACL reconstructions.

The subject of initial graft tension remains controversial, as the in situ forces in the ACL during daily activities are unknown. In addition, the significance of the viscoelastic behavior of ACL replacement grafts has not been entirely characterized. Graft tension can significantly de-
Autograft as well as allograft transplants are repopulated with fibroblasts. The last stage is marked by a gradual remodeling of the graft and continuous modifications before they form a strong fibrous tissue.

After transplantation, tendon grafts undergo biologic replacement. Initially, the tendon undergoes inflammation and necrosis. The graft then undergoes revascularization and repopulation with fibroblasts. The last stage is marked by a gradual remodeling of the graft and continuous modification of its collagenous structure. There is evidence that autograft as well as allograft transplants are repopulated with extrinsic fibroblasts within 4 weeks. In an experimental dog model using allograft patellar tendon, it has been shown that an allograft is repopulated within 4 weeks with fibroblastic cells from the insertion sites. After 4 to 6 weeks, the graft is completely repopulated. Donor fibroblasts undergo cell death and are not detectable after this period of time. The tendon structure, however, serves as a template for soft tissue remodeling.

The synovium also plays an important role in ACL reconstruction. It has been demonstrated that the synovium layer grows around the graft, forming a sheath that provides blood supply to the transplanted tissue. Revascularization of the ACL graft from the proximal insertion site results in increased blood supply to the graft for up to 18 months. Biopsies of human ACL grafts have shown that there is an early inflammatory response and neovascularization within 20 days after ACL reconstruction. At 3 months, complete revascularization of the graft takes place, initiated by the surrounding vascular synovial layer. These clinical findings underline the importance of the well-vascularized synovial layer to the success of ACL reconstruction.

After ACL reconstruction, the graft undergoes restructuring of its collagen fibers and proteoglycan content. This process is known as remodeling. Whereas histologic sections of ACL grafts show a normal crimp pattern after 6 to 8 weeks, the ligament ultrastructure, the size of the collagen fibrils, and the distribution of glycosaminoglycans are significantly different from the original tissue. In both autograft and allograft tissue, the extracellular matrix shows a distinctly different pattern between the normal ACL and the patellar tendon graft.

Graft fixation is another important factor in cruciate ligament reconstruction. The bone-patellar tendon-bone graft allows rigid fixation of the bony ends within the osseous tunnels, and healing is believed to be similar to fracture healing. Soft tissue tendon grafts, such as the quadruple semitendinosus/gracilis tendon graft, have a different healing process, with tendon healing within an osseous tunnel.

With the advent of accelerated rehabilitation after ACL reconstruction, the demand for higher fixation strength to withstand early mobilization has also increased. Fixation of replacement grafts can generally be divided into direct and indirect methods. Direct fixation devices include interference screws, staples, washers, and cross-pins. Indirect fixation devices include polyester tape-titanium button and suture-post. Significant research has been performed to determine the stiffness and ultimate tensile load of these devices. The ultimate tensile loads of these fixations range between 200 and 1600 N (Table 2).

Interference screw fixation is the most popular fixation method for bone-patellar tendon-bone grafts. Many research studies have been performed to evaluate the significance of screw size, divergence, and direction of placement. Studies have shown that screw divergence can significantly affect the ultimate failure load. Screws placed parallel to the bone block have higher ultimate
TABLE 2

<table>
<thead>
<tr>
<th>Type of fixation device</th>
<th>Ultimate tensile load (N)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single polyester tape loop</td>
<td>375 ± 8</td>
<td>104</td>
</tr>
<tr>
<td>Double polyester tape loop</td>
<td>612–651</td>
<td>84, 104</td>
</tr>
<tr>
<td>Single loop 5 Ethibond</td>
<td>238 ± 3</td>
<td>104</td>
</tr>
<tr>
<td>Double loop 5 Ethibond</td>
<td>463 ± 18</td>
<td>104</td>
</tr>
<tr>
<td>Direct soft tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metal interference screw (7 mm)</td>
<td>242 ± 90</td>
<td>20</td>
</tr>
<tr>
<td>Bioabsorbable screw (7 mm)</td>
<td>341 ± 163</td>
<td>20</td>
</tr>
<tr>
<td>Bone mulch screw</td>
<td>1126 ± 80</td>
<td>72</td>
</tr>
<tr>
<td>Tandem soft tissue washers</td>
<td>768 ± 72</td>
<td>72</td>
</tr>
<tr>
<td>Cross-pin technique (animal)</td>
<td>725–1600</td>
<td>22</td>
</tr>
<tr>
<td>Suture-post (animal)</td>
<td>374</td>
<td>78</td>
</tr>
<tr>
<td>Direct bone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metal interference screw (7 mm)</td>
<td>640 ± 201</td>
<td>81</td>
</tr>
<tr>
<td>Metal interference screw (9 mm)</td>
<td>276–436</td>
<td>59, 75</td>
</tr>
<tr>
<td>Metal interference screw (11 mm)</td>
<td>302</td>
<td>75</td>
</tr>
<tr>
<td>Metal interference screw (13 mm)</td>
<td>322</td>
<td>75</td>
</tr>
<tr>
<td>Metal interference screw (15 mm)</td>
<td>328</td>
<td>75</td>
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<tr>
<td>Bioabsorbable screw (7 mm)</td>
<td>330–418</td>
<td>81</td>
</tr>
<tr>
<td>Bioabsorbable screw (9 mm)</td>
<td>565</td>
<td>59</td>
</tr>
<tr>
<td>Staples</td>
<td>588</td>
<td>32</td>
</tr>
</tbody>
</table>

*Experiments were performed on human cadaveric knees unless specified.

Ultimate tensile loads than diverging screws. In a porcine study, screw divergence of more than 15° lowered the ultimate tensile load up to 50%. On the other hand, no significant differences in ultimate failure load have been demonstrated with changes in interference screw diameter. In recent years, bioabsorbable screws have been introduced. With the improvement in the material properties as well as screw design, the pull-out strength of bioabsorbable screws is comparable with their metal counterparts, providing an alternative for graft fixation.

Significant research has been performed on the ultimate tensile load of various fixation devices. Readers are cautioned that some of these studies were performed on cadaveric knees from elderly donors or animal models that may not represent the ultimate tensile load of the device when used clinically. Nevertheless, these studies provide comparison data regarding different fixation methods (Table 2).

**GRAFT TUNNEL MOTION**

Traditional focus on the biomechanical properties of fixation devices has been on the ultimate tensile load and pull-out strength. However, the stiffness, the amount of graft motion within the osseous tunnels, and the effects of cyclic loading on the graft construct are also important variables.

**Longitudinal Graft Tunnel Motion**

The cyclic behavior of the soft tissue graft construct is another variable in ACL reconstruction. A fixation device can have adequate ultimate tensile load but a low tensile stiffness that may compromise healing. Longitudinal graft tunnel motion (bungee effect) describes motion of the graft along the axis of the osseous tunnel (Fig. 4). A recent cadaveric study characterized hamstring tendon graft tunnel motion when using a polyester tape-titanium button technique for femoral fixation.46 Graft tunnel motion of 1 to 3 mm occurred under physiologic loading of 100 to 300 N, with the majority of motion contributed from the polyester tape loop. Graft tunnel motion can be reduced with the use of a shorter length of polyester tape loop and a longer portion of graft material within the osseous tunnel.

**Sagittal Graft Tunnel Motion**

Graft motion can also occur in the sagittal plane when the graft moves anteriorly and posteriorly within the osseous tunnel, especially during knee flexion and extension. This motion is also known as the windshield wiper effect. The magnitude of this sagittal motion can theoretically be increased with fixation of the graft distant to the joint line or osseous tunnel entrance. A number of studies have been performed to demonstrate the importance of this variable in ACL reconstruction (Fig. 5).12 In a porcine ACL reconstruction study, graft fixation that was distant to the joint line resulted in significantly more anterior laxity than did graft fixation near the joint line. On the contrary, in a prospective clinical study, anatomic fixation near the joint line for bone-patellar tendon-bone graft ACL reconstruction was compared with nonanatomic fixation that was distant to the joint line. This 18-month study showed no difference in objective and subjective stability; however, distant fixation did result in a higher incidence of bone-tunnel widening. Long-term follow-up is needed to demonstrate the significance of these findings.

**Tunnel Expansion**

Tunnel expansion seems to occur with both bone-patellar tendon-bone and hamstring tendon grafts (Fig. 6). The radiolucency associated with this phenomenon is the apparent result of bone resorption in the insertion site area. This finding is supported by MRI data showing fluid signal rather than bone signal surrounding the tendon. To date, the clinical significance of this finding is unknown. The presence of bone resorption at the graft insertion site as early as 3 months after ACL reconstruction is a disturbing phenomenon that needs to be followed closely.

**BIOLOGY OF INSERTION SITE HEALING**

The normal insertion site anatomy of the ACL has a specific arrangement of collagen fibers, fibroblasts, fibrochondroblasts, and osteoblasts forming a direct ligament insertion. The typical architecture of a direct ligament insertion consists of four layers (Fig. 7). The first layer comprises the ligament proper. The second layer is characterized as a nonmineralized cartilage zone containing fibrocartilaginous cells aligning themselves within the collagen bundles. The third layer is the mineralized cartilage zone. In this region, the fibrocartilage is mineralized and inserts into the subchondral bone plate, the fourth layer, to which the ligament is attached. This specific insertion
site anatomy is designed to distribute longitudinal and shear forces from the ligament proper into the subchondral bone plate, thus minimizing stresses on individual collagen bundles. This complex anatomy, however, is not restored by conventional free tendon transfers within the first 6 months after graft implantation. Direct implantation of tendon within a bone tunnel yields a soft tissue fixation predominantly composed of fibrous tissue aligned along the load axis. After 6 weeks, collagenous fibers can be seen protruding from the collagen fibers of the graft through the fibrous tissue into bone, thus anchoring the tendon transplant directly into the cancellous bone.

Anterior cruciate ligament insertion site healing has been evaluated in animal studies. Studies involving ACL reconstruction in rabbits using a free semitendinosus ten-
FUTURE DIRECTIONS OF ACL RECONSTRUCTION

Recent emphasis in research has been directed toward understanding the importance of the ACL in vivo as well as the rehabilitation and healing process after ACL reconstruction. Biomechanical analysis of the ACL and ACL-reconstructed knees has traditionally been evaluated in cadaveric studies. The results of these studies are extremely useful; however, their application can be limited without the information of their behavior in vivo. Significant effort has been directed toward obtaining in vivo biomechanics regarding the ACL and ACL-reconstructed knees. In vivo strain measurements\(^2\) and gait analysis\(^17,66,109\) can provide valuable information that can be used in modifying rehabilitation protocols, surgical approaches, and preoperative planning. This information may also allow us to have more thorough evaluation of ACL-reconstructed knees.

Another focus of orthopaedic research has been the application of technology in molecular biology to accelerating and promoting soft tissue healing. Growth factors have been identified as specific signaling molecules that lead to changes in the proliferative and migratory behavior of various cells. A recent study has shown that growth factors such as the basic fibroblast growth factor, transforming growth factor-\(\beta\), and the platelet-derived growth factor can promote the healing response of ligaments both in vitro and in vivo.\(^44,89\) Promising reports have also been published on the enhancement of ligament insertion site healing after the application of growth factors known as growth differentiation factors.\(^112\)

Although some success has been demonstrated with direct application of growth factors to ligament injuries in animal experiments, there are problems associated with direct delivery. These problems include short-term action and an exceedingly high local concentration of proteins. The development of delivery techniques has been aimed at achieving continuous, local delivery of growth factors. Gene therapy has emerged as one of the more promising approaches to overcome this problem. By using viral or nonviral vectors, the genetic information encoding the protein of interest is inserted into a live cell. The genetically modified cell has the potential to express the protein of interest in a sustained manner. This gene-transfer method is a potential vehicle for targeted, long-term delivery of protein to the healing ACL.\(^26,35\)

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