The Future of Knee Ligament Surgery

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Abstract

Approximately 100,000 anterior cruciate ligament (ACL) reconstructions are being performed every year in the United States alone. Long-term clinical outcome can still not exceed 85 – 90% as a result of biological, biomechanical, and technical reasons. Biological incorporation of grafts in bone tunnels (bone-to-bone and bone-to-tendon healing) is still not completely understood and is currently subject of basic science research. Knowledge on *in situ* forces and *in vivo* strains in the ACL are the basis of rehabilitation regimens. Ultimately, healing and remodeling of the ACL graft needs to be improved. Gene therapy can be applied to the field of Orthopaedic Surgery by transfer of defined genes encoding for growth factors into target tissues (e.g. ligament, cartilage or bone). Local cells at injury sites can then highly and persistently produce therapeutic proteins. Gene transfer techniques in animal models have shown promising first results when enhancing graft incorporation. In addition, Computer Assisted Orthopaedic Surgery (CAOS) is now considered to add further precision and accuracy to knee ligament surgery. Passive and active systems are thereby distinguished. In the future, a simple muscle biopsy may be enough to provide the cell that can restore any kind of defect in the knee by growing the local cell line. With improved medical imaging techniques and surgical robotics, clinical outcome may be improved. [Acta Clinica 2:101-107]

Keywords: anterior cruciate ligament; knee; reconstruction; biomechanics; gene therapy; tissue engineering

Introduction

A large number of anterior cruciate ligament (ACL) reconstructions are being performed each year around the world (estimated between 75,000 to 100,000 cases in the United States alone), however the question remains: „how perfect are current operative techniques?" Numerous techniques have been introduced to the literature, but success rates for long-term clinical outcome can still not exceed 85 – 90%. The global perspective on ACL reconstruction shows that more then 20 different surgical techniques are available today, that more then five different grafts are currently being used with different rehabilitation protocols and different outcome assessments. At the recently held Panther Sports Medicine Symposium (Pittsburgh, PA, USA, May 4 – 6, 2000), 14 specialists in knee ligament reconstruction presented their graft choice and preferred technique for ACL reconstruction on a global panel consisting of experts from five continents. Interestingly, about 50% of the experts were in favor of the hamstring tendons, 50% preferred the B-PT-B graft, and two-thirds of the surgeons use multiple grafts. There was a discussion about several possibilities for fixation of grafts that have undergone an evolutionary process in the past two decades. Especially for hamstring tendons we still have not found the perfect solution yet. However, talking about different grafts keeps us from addressing the real dilemma: „the perfect graft does not yet exist!" This perfect graft would reproduce insertion sites and biomechanics, provide biological incorporation, and resume neuromuscular control.

Biomechanics

During the last decade, significant efforts have been made to quantify the forces and strains in the ACL in *in vitro* as well as *in vivo*. As a result, various devices and methods have been developed to measure the force and strain in ligamentous tissue. In our laboratory, we have successfully used

a 6-degree of freedom (DOF) universal force moment sensor (UFS) in combination with a 6-DOF robotic manipulator to measure the *in situ* force of the ligament. Forces and distributions in both the AM and the PL bundle of the ACL have been quantified during the anterior drawer test, Lachman test and simulated pivot shift test using human cadaveric knee specimens. We learned that a tibial graft fixation nearest the articular surface resulted in a more stable knee and closer *in situ* forces to the intact ACL. We also found that the position of the tibia during graft fixation had a significant effect on the biomechanical outcome. Two popular grafts for ACL reconstruction, quadruple semitendinosus/ gracilis (hamstrings) and bone-patellar tendon-bone were studied. Both were found to have little improvement over the ACL deficient knee when rotational loads were applied. Whereas, an anatomical reconstruction replacing the AM and PL bundles resulted in knee kinematics significantly closer to those in the intact ACL as compared to conventional reconstruction procedures. Additionally, the *in situ* forces in the anatomical reconstruction were substantially closer to those of the intact ACL compared when the knee was subjected to both the Lachman and simulated pivot shift tests. However, what we still need are in-vivo forces in ligaments to reveal which postoperative rehabilitation protocol is the most effective in loading the ACL graft but not exceeding the fixation strength. Furthermore, knowledge of in-vivo forces of the ACL will enable us to examine the function of the ACL grafts by comparing the force data with those for the intact ACL – which we consider as the „true gold standard" to achieve for ACL reconstruction.

Biology

Normal insertion site anatomy of the ACL has a specific arrangement of collagen fibers, fibroblasts, fibrochondroblasts and osteoblasts forming a direct ligament insertion, which consists of four layers. The first layer comprises the ligament, the second layer is characterized as a nonmineralized cartilage zone containing fibrocartilaginous cells, the third layer is the mineralized cartilage zone, where the mineralized cartilage inserts into the subchondral bone plate, the fourth layer, to which the ligament is attached. The design of this complex insertion site allows for distribution of longitudinal and shear forces from the ligament into the subchondral bone plate, thus minimizing stress on single collagen bundles. This complex anatomy, however, is not restored by conventional ACL-transplantations within the first six month after graft implantation.

After ACL-reconstruction, tendon grafts undergo biologic modifications before they form strong fibrous tissue. In the beginning, the graft undergoes inflammation and (partial) necrosis. The graft then undergoes revascularisation 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 four weeks.

After four to six weeks, the graft is completely repopulated. Donor fibroblasts undergo cell death and are not detectable thereafter. The tendon structure, however, serves as a template for soft tissue remodeling.

While the biology of healing of the ACL replacement graft is grossly the same for all biologic graft materials, graft fixation remains problematic. Grafts with bone plugs on either side (bone-patella tendon-bone (BPTB), quadriceps tendon) allow for bone-to-bone healing within the bone tunnels. Soft tissue grafts, however, such as the quadruple semitendinosus/gracilis tendon graft, have a different healing

process, with tendon-to-bone healing within the bone tunnel. With the advent of accelerated rehabilitation after ACL reconstruction, the demand for higher fixation strength to withstand early mobilization has also increased. For hamstring tendons, there are numerous fixation devices available, endobutton, cross pin, staple, suture post are some of them. Bioabsorbable screws have been introduced in recent years and the material properties are comparable with metal interference screws. Bioabsorbable screws can lead to an accelerated tendon-bone healing with a press-fit fixation of hamstring tendons in the bone tunnels, however, the fixation of the tendon is at risk by time of bio-absorption of the screw and can be a potential cause of failure.

Biological Solutions

Presently, no graft can reproduce the normal insertion sites and grafts undergo a certain remodeling process. The question remains how to improve healing and remodeling. Among the different methods developed for local administration of growth factors, gene transfer techniques have been proven to be the most promising.

Gene therapy is a technique that relies on the delivery of therapeutic genes into cells and tissues. Originally, gene therapy was conceived for the manipulation of germ-line cells for the treatment of inheritable genetic disorders, however this method is limited to not yet efficient technology and considerable ethical concerns. Gene therapy can be applied to the field of Orthopaedic Surgery by transferring of defined genes encoding for growth factors or antibiotics into a target tissue (e.g. ligament, cartilage or bone). Thus, local cells at the injury site can highly and persistently produce therapeutic substances.

For gene expression, the transferred DNA material has to enter the nucleus, where it either integrates into the chromosomes of the host cells or remains episomal. After transcription, the generated mRNA is then transported outside the nucleus, serving as a matrix for the production of proteins (e.g. growth factors) in the ribosomes. Consequently, the transduced cells become a reservoir of secreting growth factors and cytokines capable of improving the healing process. Viral (e.g. adenovirus, retrovirus) and non-viral (e.g. liposomes, gene gun) vectors can be used for delivery of genetic material into cells.

Tissue engineering based approaches that aim at using cells from different origin tissues (e.g. mesenchymal stem cells, muscle derived stem cells or dermal fibroblasts) to deliver genes might offer additional opportunities to improve the healing process. Selecting the appropriate gene delivery procedure depends upon various factors such as the division rate of the target cells, pathophysiology of the disorder and the accessibility of the target tissues.

Computer Assisted Orthopaedic Surgery

Computer Assisted Surgery (CAS) may allow surgeons to be more precise and enduring. Medical imaging, such as magnetic resonance and computed tomography is not only an important diagnostic but a necessary planning tool. In ACL reconstruction procedures for example, tunnel positions are crucial, especially when placed outside the anatomical attachment area. Despite this knowledge however, the rate of misplaced tunnels in ACL reconstructions has been reported between 10 – 40%. CAS is now assumed to lead to more precise tunnel placement. Two types of CAS systems, passive and active systems have been developed. Passive systems, or surgical navigation systems provide the surgeon with additional information prior to and during the surgical procedure (in real time). Active systems have the ability of performing certain surgi-

cal steps autonomously. Both active and passive CAS systems are currently subject of basic science and clinical investigations and will be discussed and commented on in this article. In summary, passive navigation systems can provide additional information to the surgeon and can therefore lead to more precise tunnel placement. Active robotic technology seems to be accurate and feasible with promising initial results from Europe. However, CAS can only be as precise as the surgeon who plans the procedure, therefore future studies have to focus on integrating, arthroscopy, 3D image-enhanced computer navigation, and surgical robotics to increase precision in surgical techniques.

Perspectives

In the future, improvement of biological incorporation of replacement grafts will lead to better insertion site healing as well as faster ingrowth of the graft. Gene therapy, cell therapy, and tissue engineering are the possible biological tools. It will be possible to deliver therapeutic genes, encoding growth factors, such as BMP-2, TGF-ß, etc. into cells and tissues. Furthermore, the application of certain growth factors can create any graft type that does enhance biological healing, insertion site incorporation, and restores nerve and vascular function. One focus can be the gene-based cell therapy approach that is based on the ability of mesenchymal stem cells (from blood, bone marrow or muscle) to divide into a variety of cell types. In the future, a simple muscle biopsy may then be enough to provide the cell that can restore any kind of defect in the knee (cartilage) by growing the local cell line (chondrocytes). However, we have to take safety issues into consideration. A new therapeutic approach that might be extremely promising needs to undergo extensive animal study prior to application on humans.

Additionally, surgical techniques need to be perfected. Improved imaging techniques and computer-assisted orthopedic surgery (CAOS) will enhance both surgical precision and pre-operative evaluation. Advantage can thereby be taken of passive navigation systems (Knee Nav®, Pittsburgh, USA) as well as active robot systems (CASPAR®, Rastatt, Germany). Using these newly developed tools we expect to gain more precision in tunnel placement of ACL reconstructions. However, both systems, active and passive, rely heavily on preoperative planning and accurate imaging. But we have to understand that the computer-assisted surgery will only be as precise as the surgeon who plans it. Computer-assisted orthopedic surgery, improved precision, and technical enhancement will again reduce the risk of error in surgery.

In the year 2020 we will have improved biomechanical knowledge, sophisticated biological tools, and user-friendly computer-assisted surgery. There is a good chance that a biological/ tissue engineered graft will be available. However, in the year 2001, the surgeon still has to focus on perfecting the surgical technique as well as adjusting the rehabilitation protocol to the individual patient. Essentially, a surgeon who performs less then 30 ACL reconstructions per year should use one technique and graft. In contrast, if the practice is more then 50 – 60 cases a year, the surgeon should hopefully be familiar with several techniques and grafts and apply them according to the patient's needs and interests. In the clinical protocol in Pittsburgh, about 50% Bone-Patella Tendon-Bone, 45% hamstring tendon autografts, and 5% allografts are being used in the year 2001. This varies according to patient requirement. However, in the next decade, the difference in grafts will be less pivotal as biological and biomechanical advancements continue to evolve.

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