Looking Into Ways to Enhance the BEAR Method for ACL Repair

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Abstract

Anterior cruciate ligament (ACL) tears are the most common knee injury with major consequences. The limitation to one's knee movement restricts one from everyday physical activities and exercises, which can lead to serious mental health impacts. The current surgical method commonly used, called the ACL reconstruction has limitations, calling attention to the need for improved surgical methods. A new surgery technique, the Bridge-Enhanced ACL Repair (BEAR) method now exists, which utilizes a collagen implant in replacement of a graft. This review summarizes the current BEAR method and proposes ways to improve it using cells called fibroblasts. The goal is to shorten the recovery period following ACL tears, so that patients can rehabilitate and return to their usual activity as soon as possible.

Introduction

The anterior cruciate ligament (ACL) is the most commonly injured ligament in the United States, with 400,000 ACL repair surgeries occuring every year (Evans et al.). The ACL is an important part of the body, as it stabilizes the knee joint by preventing the shin bone (tibia) from moving too far forward compared to the thigh bone (femur). This limits rotational knee movements (Yoo and Marappa-Ganeshan). The ACL is located behind the kneecap and forms a cross shape with another ligament called the posterior cruciate ligament (PCL) (Fig 1). Despite forming a cross shape together, ACL injuries are more common than PCL injuries. In one study, PCL injuries occurred in one every 55,555 people, while ACL injuries occurred in one every 1,457 people (Vaishya et al.). For ACL injuries, the highest risk age groups are males between 19 and 25 years old and females between 14 and 18 years old due to active participation in physical activities, especially athletics (Sanders et al.). Injuries occur when the tibia is displaced anteriorly compared to the femur while the knee is flexed (Evans et al.). Female athletes are 4.5 times more likely to tear their ACL than males. Some studies suggest this is because females are more quadriceps dominant (Evans et al.). Flexing the quadricep muscle to slow down puts stress on the ACL (Evans et al.). Since the knee is required for most lower extremity movement, including jumping and changing direction, a functional ACL is crucial for daily life (Evans et al.).

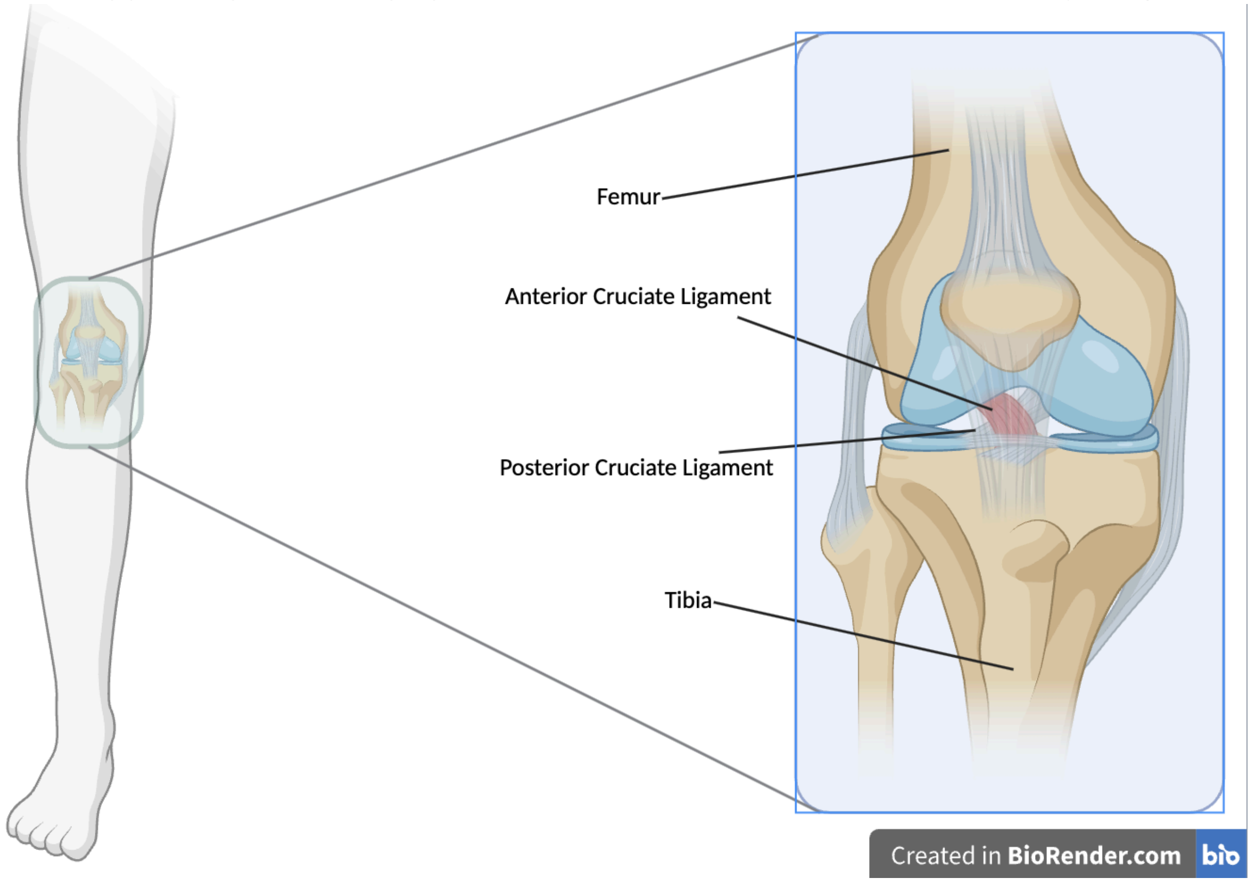

Fig 1: The ACL anatomy. The picture on the right is a zoomed in picture of the ACL. The red highlighted ligament is the ACL, which is in front of the PCL hence called anterior. The femur is the thigh bone and the tibia is the shin bone. The ACL mainly stabilizes these two leg bones and holds them together. Body parts that are used frequently, like ligaments, have an increased risk of getting injured. Torn ligaments poorly heal on their own, unlike broken bones which are highly vascularized.

Currently, ACL injuries are repaired by a surgical process called reconstruction. As the name suggests, autograft or allograft tissues are used to connect the tibia and femur together (Fig 2). In some cases, double bundle procedures are performed, where a single bundle of ACL is replaced with two bundles, a repaired ACL and a hamstring autograft, for additional stability. Although the success rate is as high as 85% (Friedman et al.), there are many risks with graft harvesting. Excessive removal of muscles from graft harvesting can result in weakness in the area. For example, excessive removal of a hamstring graft can lead to knee flexion weakness. Additionally, inadequate release of the graft can cause proximal transection of the tendon. This occurs when the graft is cut short, leaving some of the tendon behind. The body part in which the graft was taken will be damaged because of the leftover. Moreover, damage to the saphenous nerve can lead to pain and burning sensations (Tjoumakaris et al.). In addition to graft harvesting risks, there are possibilities of re-injuring the same ACL which is weakened secondary to the tear. In fact, in one study with 315 patients, the retear rate was 18% (Webster and Feller). ACL injuries lead to many other negative consequences. Limitation to both general exercises and sports can harm one's mental health. Lastly, half of individuals with ACL tears later go on to develop osteoarthritis (degeneration of joints), which can lead to pain and swelling of the knee (Rodriguez-Merchan and Encinas-Ullan). Because independence is a key factor to one's quality of life, inability to perform those tasks can have a negative impact on one's mental health (Burckhardt and Anderson).

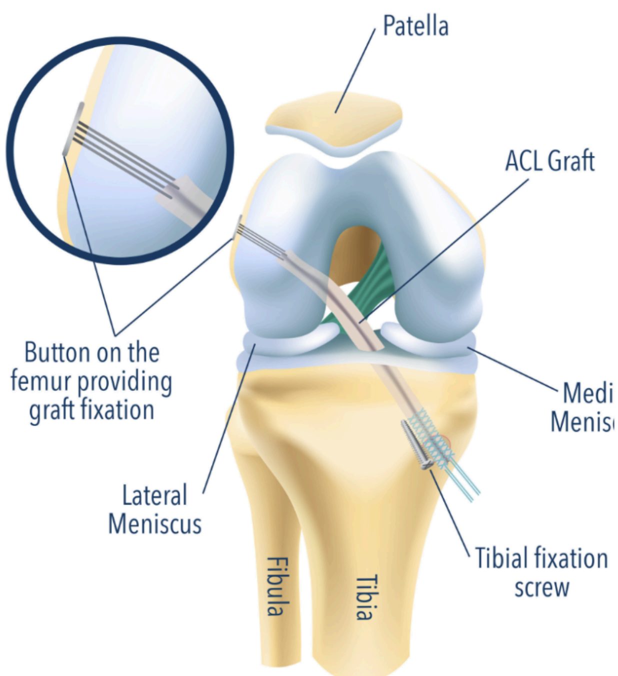

Fig 2: The ACL Reconstruction. After a torn ACL, an autograft or allograft is used to place in between the two torn parts of the ligament. The graft is connected both to the original ligament and to the femur and the tibia for additional stability ("The ACL Injury Guide - A Guide for Patients about ACL Injuries and ACL Surgery").

This paper explores a new alternative method to ACL reconstruction called the BEAR method. I then discuss ways that the BEAR method can be improved by the addition of fibroblasts to help shorten the recovery period following ACL tears. It also explores how to measure the success of new ACL surgery methods. This paper focuses on grade 3 tears, which is the most severe form of ACL injuries.

The BEAR Method

Bridge Enhanced ACL Repair (BEAR) is a new surgical method approved by the FDA in 2020 (Commissioner). This method uses a hydrophilic, bovine-derived extracellular matrix collagen bridge between the separated ligament (*Bridge-Enhanced ACL Repair (BEAR) Allows Torn ACL to Heal Itself | Duke Health*) (Fig 3). Compared to standard ACL reconstruction surgeries, this method is less invasive as there is no need to open another surgical spot to replace the ligament. A graft taken from one part of the body for another part of the same person's body is an autograft. Conversely, the BEAR method uses an arthroscope to place the BEAR implant, made out of bovine collagen, from 2-3 small cuts around the knee (Commissioner). Additionally, because no foreign tissue is used, rejection is decreased. The BEAR implant is also injected with blood as a growth factor (Commissioner). The blood clots activate cell migration and proliferation (*Bridge Enhanced ACL Restoration (BEAR)*). This is due to the ability of fibroblasts, a cell type found throughout the body, to react to the blood and assist with healing. To ensure the collagen is absorbed by the body, it is stabilized by stitching the implant to both the tibia and femur ligament. A final stitch is placed to stabilize the structure.

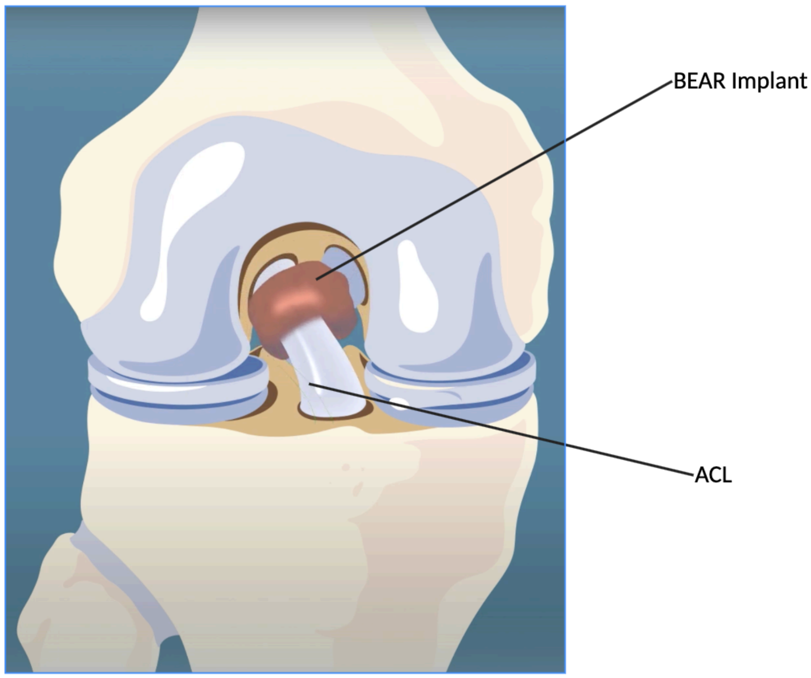

Fig 3: The BEAR Method: This method uses a hydrophilic, bovine-derived extracellular matrix collagen bridge (BEAR Implant) between the torn ligament. The patient's blood is absorbed by the implant to allow blood clots to form and accelerate the healing process. Stitches are used to stabilize the connection between the implant and the leftover ligament (Duke Health).

Not only is this procedure non-invasive, but it also has promising results. ACLs repaired by traditional reconstructions had a hamstring muscle strength index of 56% to 64%, while the BEAR method had 90% to 99%, at 24 months (Murray, Kalish, et al.). Hamstring muscle strength index is a ratio between the strength of the hamstring to the strength of the quadriceps. The higher the percentage, the more strength the hamstring has to bend the knee without rupturing the ACL. Time to recovery also decreases with the BEAR method. For a group of 100 people, when either BEAR method or the traditional method was selected, 88% of BEAR method repairs went back to their activity after a year, while the traditional method was 76% (Barnett et al.). Allowing athletes to go back to their sports more quickly at the level they used to be, greatly contributes to their mental health too.

On the other hand, there are some limitations to the BEAR method. First, the surgery needs to be performed within 50 days of the injury (*Bridge-Enhanced ACL Repair (BEAR) Allows Torn ACL to Heal Itself | Duke Health*). while the traditional method can be performed up to 6 months after injury[15]. Additionally, with the BEAR method, the patient needs to be 14 years or older (Commissioner), whereas for the reconstruction it has been done to a patient as young as 9 years old (Baghdadi et al.). BEAR method failure rates were high for younger patients due to developing growth plates (Barnett et al.). Lastly, the BEAR method needs more than 50% of the tibial stump in continuity (10mm of tibial and 5mm of femoral stump), while reconstructions have no limit (*Bridge-Enhanced ACL Repair (BEAR) Allows Torn ACL to Heal Itself | Duke Health*).

Improving the BEAR method using fibroblasts

The new method that will be explored in this review paper will introduce fibroblasts, derived from skin biopsies, to the BEAR method (Tremblay et al.). From a past study where skin biopsy derived fibroblasts were used for ACL repairment in goats, it resulted in greater remodeling of the injured site and ECM synthesis (Tremblay et al.). A punch skin biopsy removes fibroblasts from the skin so they can grow in cell culture, which is typically done on the forearm (Boyd et al.). Once a local anesthesia is given to the patient, a small pencil eraser sized circular instrument called punch biopsy is used to carve out a small portion of the skin (Zuber). This portion of the skin, about 4 mm, is cut into 12 to 15 smaller pieces to be put on multiple wells of gels with Dulbecco's Modified Eagle Medium (DMEM) (Vangipuram et al.), which is used for general cell and tissue cultures. Additionally, 20% fetal bovine serum (FBS) (Vangipuram et al.), a rich source of proteins and growth factors (*The Basics of Fetal Bovine Serum Use - US*), is added to further support the culture.

However, because these are just cells multiplying with the nutrients given, without a shape, like an extracellular matrix, it cannot be utilized. So, an extracellular matrix will be utilized as a mold to grow the fibroblast into a desired shape. In the BEAR method, BEAR implant is a rectangle box and is attached to the tibial stump with supports. These attachment sites (the thigh side and the knee side) are where the tissues come together. By wrapping fibroblasts around the attachment site, it might ease the attachment process. However, shape is not the only thing to be considered. The environment of fibroblasts that are in the ACL is mimicked, to produce fibroblasts that are found in the actual ACL (Masson-Meyers et al.). Additionally, the ECM scaffold will be placed into the knee together with the implant, so permeability of the ECM matters for the cell proliferation and migration to occur (Masson-Meyers et al.). By culturing fibroblasts specific for the area, in this case the ACL, it ensures that fibroblasts proliferate and migrate appropriately.

The evidence to support using fibroblasts for ACL ligament repair is derived from the natural process that occurs during healing of a human wound (Shetye et al.). After a wound occurs, high expression of insulin-like growth factor 1 (IGF-1) leads to proliferation and migration of fibroblasts (Shetye et al.). Fibroblasts produce both collagen and extracellular matrix around the site until it forms a scar (Shetye et al.). This scar goes through remodeling after about three weeks, during which the scar's shape slowly returns to its original shape (Shetye et al.). Although this new area is mechanically inferior compared to the original, this goes the same for any kind of ACL reconstruction (Shetye et al.). Fibroblasts divide and replicate multiple times with a signal from platelet-derived growth factor (PDGF) (Shetye et al.). Theoretically by bringing in external fibroblasts to an injured area, the process should be faster. The quicker the patient recovers from a ligament injury, the earlier the patient can start transitioning to strength gaining exercises. This allows for functioning at the highest performance, especially for athletes (Waldron et al.).

Moreover, the BEAR method depends on the autologous blood that is injected to the BEAR implant. Because the BEAR implant is attached to the patient's tibial stump, fibroblasts from the patient's ACL interact with the blood clot from the injection to produce vital proteins, including fibronectin, and form a structural framework ("New Blood Clot Research Indicates Enhanced Understanding of Wound Repair"). In addition, studies indicate that platelets that are in blood can also form a provisional fibronectin matrix. However, instead of waiting for the fibroblasts that are essentially disconnected and apart to be attracted, fibroblast cells in liquid media can be injected with the blood to the BEAR implant (Fig 4).

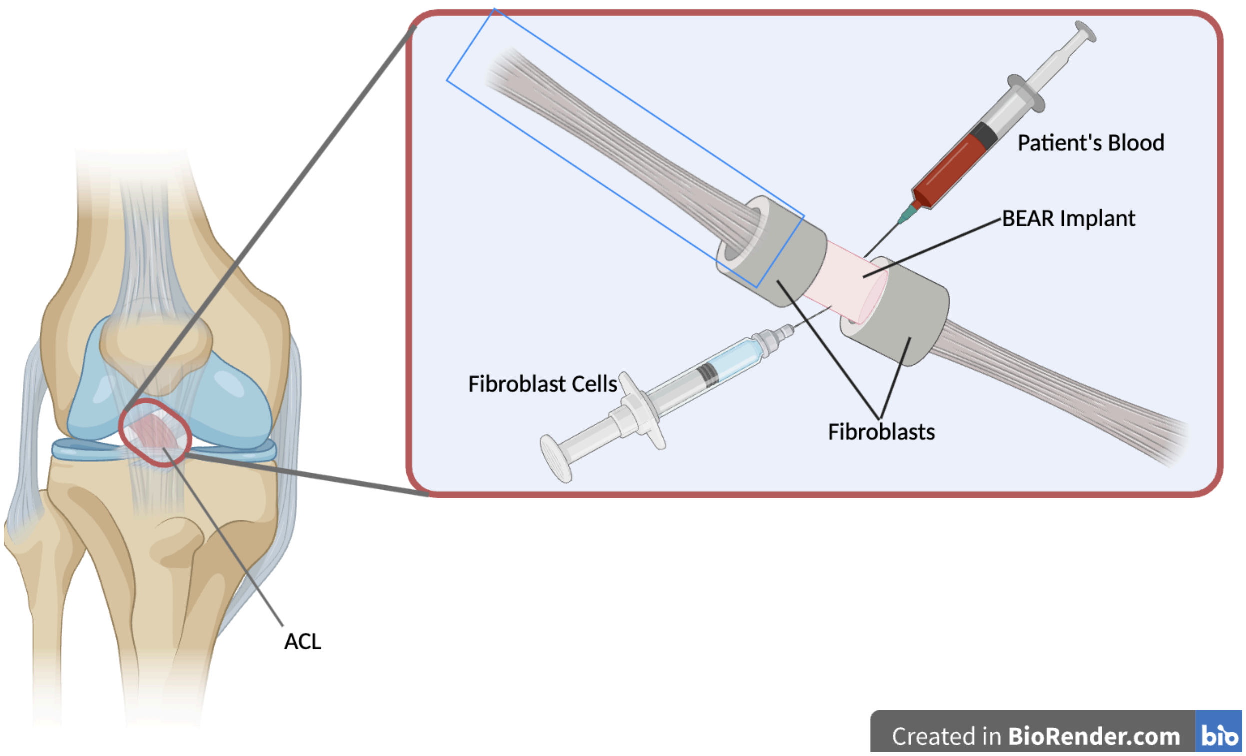

Fig 4: The BEAR Method with Fibroblast Cells: Instead of just stitching the BEAR implant to the ligament, this method wraps around the attachment site with fibroblast cells to expedite healing procedure. Additionally, by injecting fibroblast cells in liquid media, these fibroblasts can utilize the injected blood to create blood clots and eventually heal.

Outcome measures

To assess how well the new method is working, there are few things one can do to compare it with the original reconstruction method or to the traditional BEAR method. First of all, the possibility of an infection can be assessed through body temperature (>101 Fahrenheit), increasing knee pain, and effusion (liquid). Arthrocentesis (using a needle to extract synovial fluid) can be used to assess if any organisms are found for infections. If no organisms are found, but apparent signs like swelling and warmth can be felt, it is considered a mark of inflammatory reaction. During the 6-week follow-up visit, if guidance of a crutch is needed, the patient would be classified as having muscle atrophy. Lastly, MRI tests can happen at the 3 months mark to check for any tears (Murray, Flutie, et al.).

Next, there are tests to evaluate the level of success. One test talked about earlier, the hamstring muscle strength index, would require the patient to push and pull their leg as hard as possible, which would score their leg's strength. Additionally, the patient's pain scale can be also used as a reference. Finally, a unit created by the International Knee Documentation Committee (IKDC) measures the translation of the knee. The more the knee moves the lower the score will be (Murray, Flutie, et al.).

Discussion

Although there is some evidence to support this improved BEAR method, there are still some limitations. One major limitation is the timeline to use autologous cell transplants (fibroblasts). In order to get cells from the patient and grow them, it would take multiple weeks, if not months. Skin punch biopsy in total takes about 4 to 8 weeks. Because the BEAR method surgery needs to be completed within 50 days of the initial injury, punch biopsy cannot be performed on the injured patient. An alternative would be to obtain allogeneic fibroblasts. However, this takes away the advantage of the BEAR method not bringing in any foreign parts. In addition, because fibroblasts have the ability to form ECM and sometimes cannot be controlled, it can ultimately form scars which could cause pain or limit movement. Lastly, because this method has never been done before, no results of long term effects are known.

Conclusion:

Physical activity is an important part of our society and is popular from friendly competitions to professional sports. Physical workouts are a necessity for humans to stay both physically and mentally healthy. Although ACL tears are the most common knee injury, the current surgical standard of care has limitations. A new surgery called the BEAR method now exists, which utilizes hydrophilic, bovine-derived extracellular matrix collagen in replacement to a graft. This review summarized the current BEAR method and proposed ways to improve it using fibroblasts. Despite the limitations that we can come up with, there are other potential components that will be beneficial if added. First off, by using the cell reprogramming technology, modified fibroblasts that are more efficient in healing than normal fibroblasts can be produced. Additionally, because proteins can influence connective tissue cells, the ability to manipulate the cells may prevent over scarring that can damage and re-tear. It is exciting how ever-advancing technologies create new possibilities to utilize and improve surgical methods.

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