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Tissue-Engineered Grafts: The Future of Anterior Cruciate Ligament Reconstructive Surgery

Amber Braxton
amber.braxton372@my.lincolnu.edu

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Amber Braxton

Lincoln University

Outline

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Abstract

Anterior cruciate ligament (ACL) ruptures are common injuries, specifically for young athletes, and in order to repair this injury, the patients must undergo ACL reconstructive surgery. This surgery commissions the use of autografts and allografts in order rebuild the torn ligament. Traditional autografts are the patellar tendon autograft, which is the most common, and the hamstring autograft. These grafts are made by transplanting tissue from the patellar tendon or the hamstring to the ruptured ACL. Allografts are another type of graft that involves transplanting tissue from a donor cadaver to the patient. Traditional autografts and allografts have been used for years even though they have nagging side effects such as donor site morbidity, loss of muscle strength, disease transmission, and graft rejection. However, now orthopedic doctors are looking into tissue-engineered grafts in order to circumvent these problems.

Tissue-engineered grafts are made of synthetic material, such as collagen, and stem cells. Theoretically, these grafts would not have the same problems that traditional autografts and allografts have, but research has shown that tissue-engineered grafts have their own drawbacks as well. The most glaring problem with tissue-engineered grafts is that they are not very durable, so graft failure is a common side effect. Orthopedic doctors are working on ways to improve the strength of tissue-engineered grafts, but these improvements have not been successfully tested on humans yet. Therefore, as of today, tissue-engineered grafts are not recommended as a successful alternative to traditional autografts and allografts.

Introduction

Anterior cruciate ligament (ACL) ruptures are a common injury in many young athletes, and this type of injury causes players to miss an entire season of play. This injury and recovery period is detrimental to players and their teams, so orthopedic doctors are actively searching for a way to shorten recovery time, prevent reinjury, and find a better surgery method with fewer side effects (Gobbi et al. 2006). The traditional method for treating ACL ruptures is to undergo ACL reconstructive surgery using traditional autografts and allografts. Autograft transplants involve transplanting tissue from one part of the patient's body to the torn ACL. Usually, the tissue is taken from the patellar tendon in the knee or from the hamstring, and both of these autografts have proven to be effective in helping athletes recover from an ACL injury (Dhammi et al. 2015). Allograft transplants involve moving tissue from a donor cadaver to the patient's torn ACL, and this technique also helps athletes recover and return to play (Chang et al. 2003).

Traditional autografts and allografts have been used for years as treatment for ACL injuries even though they have some major flaws, such as donor site morbidity or disease transmission. However, new ACL grafts using ligament tissue engineering are being developed. This new technique for creating grafts can possibly allow athletes to recover faster from ACL injuries, and these grafts may also be able to lower the incidence of reinjury in patients (Rathbone et al. 2012). This review will study literature detailing the advantages and drawbacks of traditional autografts and allografts, and it will also review literature describing the advantages and limitations of the new grafts being developed. Comparing the traditional autografts and allografts to the newer tissue-engineered grafts will examine if the newer grafts will overall be better than the traditional.

Traditional Autografts and Allografts

When treating an ACL injury, orthopedic doctors usually recommend ACL reconstructive surgery in order to stabilize the knee. This surgery involves replacing the torn ACL with another ligament using either a patellar tendon autograft, a hamstring autograft, or an allograft from a donor cadaver (Rathbone et al, 2012). These are the most popular grafts used, but they each have their own side effects that make recovery difficult for patients.

Patellar Tendon Autograft (BPTB Graft)

The most recommended autograft is the patellar tendon autograft, and it is commonly considered the "gold standard" of grafts (Dhammi et al. 2015). The patellar tendon autograft, or the bone-patellar tendon-bone (BPTB) graft, is frequently chosen because when it has been clinically tested, it has usually had great results. The article by Dhammi et al. (2015) showed that 83% of long-term patients receiving the BPTB graft now have normal knee function, and only 1.6% of patients needed additional surgery due to failure of the BPTB graft. 83% satisfaction is a great statistic for many orthopedic doctors, but BPTB grafts also have their limitations.

Dhammi et al. (2015) also mentioned the disadvantages of the BPTB graft. Some common side effects of this graft are patellar tendon ruptures, patellar/tibial fractures, quadricep weakness, chronic anterior knee pain, difficulty kneeling, and numbness due to nerve damage during surgery. Also, in the study by Gobbi & Francisco (2015), the authors found that after performing isokinetic tests, which is a common test to determine strength of the muscles around the knee, the patients receiving a BPTB graft had significantly decreased quadricep strength 3 months after surgery compared to the other group of patients who received the hamstring autograft. This significant loss of quadricep strength was also observed in by Hiemstra, Webber, Macdonald, & Kriellaars (2000).

They found that subjects with the BPTB graft had decreased knee extension strength that was not seen in the study group receiving the hamstring graft. Loss of knee strength is one of the main reasons why it takes so long for athletes to recover from ACL injuries because they must take time to rebuild their muscle strength. The BPTB graft seems to exacerbate this problem.

Hamstring Autografts

Although the bone-patellar tendon-bone graft is very popular, the hamstring autograft is becoming a highly recommended alternative. The hamstring autograft usually involves transplanting the semitendinosus tendon from the hamstring of the patient to replace the torn ACL, or surgeons can also remove the gracilis tendon with the semitendinosus tendon, which is also located in the hamstring (Dhammi et al. 2015). The main advantage the hamstring autograft has over the BPTB graft is that chronic knee pain is greatly reduced after surgery. Hamstring autografts also have a lower risk of failure compared to the common BPTB graft, and the quadricep muscle is much stronger when the hamstring autograft is harvested (Hiemstra et al. 2000). However, the hamstring autograft also has its drawbacks.

Dhammi et al. (2015) showed that some of the major disadvantages of the hamstring autograft are greatly reduced knee flexion strength, sciatic nerve palsy, and inferior fixation strength. Also, Clatworthy, Bulow & Bartlett (1999) found that there was significant tunnel widening in patients receiving the semitendinosus and gracilis grafts, which was not found in patients receiving the BPTB graft. Tunnel widening prevents the tendon from healing properly to the bone, and it is also associated with anterior knee laxity. It has also been implicated as a major cause for graft failure, which can lead to revision surgery to fix the failed hamstring graft (Srinivas, Kanthila, Saya, & Vidyasagar, 2016). Hamstring autografts also result in decreased hamstring strength when compared to BPTB grafts 3 months after surgery (Gobbi &Francisco, 2015). Therefore, even though hamstring grafts have many advantages compared to the BPTB grafts, they are far from perfect.

Allografts

Autografts have been used and highly recommended for years, but their major disadvantage is donor site morbidity, which is where the site of the extracted graft becomes weakened, stiff, and sore. Allografts, on the other hand, do not have this side effect, which is why they are growing in popularity. Allografts involve transplanting the patellar tendons, the hamstring tendons, and Achilles tendons from a donor cadaver to a patient with a torn ACL (Dhammi et al. 2015). One of the main advantages of allografts is that there is no harvest site damage because the tendon was not removed from the patient. Surgery time is also shorter, and post-operative recovery is a lot easier (Dhammi et al. 2015). In a study by Cole et al. (2005), the authors also found that ACL reconstructive surgeries using allografts are much more cost efficient than surgeries involving BPTB autografts. They averaged about $1,000 less than the ACL reconstructive surgeries using patellar tendon autografts.

Allografts cost less money, and they offer a plethora of advantages not seen in patellar tendon autografts and hamstring autografts. However, there are also some major disadvantages when using allografts. The main limitations of allografts include disease transmission, delayed graft incorporation, potential immune reactions, and tunnel widening (Chang et al. 2003). Disease transmission is quite possibly the most dangerous disadvantage of allografts. HIV and hepatitis C can possibly be transmitted to a healthy patient because of an allograft, and there have also been a few documented cases of sepsis occurring after an allograft transplant (Chang et al. 2003). Also, since the allograft was removed from a cadaver, there is a chance that the tissue may be rejected by the patient's immune system (Dhammi et al. 2015). However, with new and advancing knowledge about certain diseases and new rejection medicines, the risk of disease transmission and graft rejection from an allograft is becoming less common. Still, it is a risk that makes many patients hesitant to get allografts over patellar tendon autografts and hamstring autografts.

Summary

Patellar tendon autografts, hamstring autografts, and allografts from a donor cadaver have been used for a long time. They each have certain advantages and disadvantages that make them mostly equal when it comes to determining which graft works the best, although the patellar tendon autograft is still the most highly recommended (Dhammi et al. 2015). However, orthopedic doctors and surgeons are developing new alternatives to the traditional autografts and allografts. One of these alternatives involve tissue ligament engineering, which could be the future of ACL reconstructive surgery.

New Tissue-Engineered Grafts

Tissue-engineering combines science, engineering, and medicine in order to create cells *in vitro* that can possibly grow and develop into a fully functioning tissue. Tissue-engineering was originally industrialized to fix skin, cartilage, and bone damage, but now doctors are considering it in order to produce a synthetic ACL (Rathbone et al. 2012). In order to produce a functional tissue-engineered ACL, it is important to search for the right material that will mimic the structure of a human ACL. Collagen has been extensively studied to create a synthetic ACL (Vavken, Joshi, & Murray, 2009), and other prosthetic ACL's have been developed using polytetrafluorethylene, polyester, and polypropylene ligament augmentation devices (Patinharayil, 2017). However, the results from the use of these are not very promising.

Even though synthetic ACLs were tested on human subjects and failed in the late 1970s and 1980s, they are still being studied closely as an alternative to traditional autografts and allografts (Patinharayil, 2017). Technology has advanced since then, so better synthetic ACLs are being developed. By using the appropriate cells, such as stem cells and primary fibroblasts, and by finding the appropriate biomimetic scaffold to design the engineered ACL, it is possible to make a functional tissue-engineered ACL (Yates et al. 2011). While these newly developed synthetics have yet to be tested on humans, a bio-enhanced scaffold treated with platelet-rich plasma was tested in animal ACLs, and there was significant improvement of mechanical and biological healing of the ruptured ACL (Nau & Teuschl, 2015). Along with some successful animal testing, Triton-X, a common detergent used in laboratories, was treated on ACL tissue, and there was efficient decellularization of the tissue without major changes to the foundation of the tissue. Decellularization could effectively prevent remodeling of the tissue-engineered ACL, and it could also prevent tunnel widening and graft rejection so that the tissue-engineered ACLs will be more functional in human subjects (Vavken et al.2009). Although there is more research and testing to be done on tissue-engineered grafts, new developments in the study of tissue-engineering could eventually yield a tissue-engineered ACL that could potentially rival the traditional autografts and allografts. However, this does not necessarily mean that they will overall be better than traditional grafts once they are tested on humans.

Tissue-Engineered Grafts vs. Traditional Grafts

Although traditional autografts and allografts have been used for years, orthopedic doctors are still actively searching for a better type of graft with fewer side effects for ACL patients. As mentioned earlier, one of the main problems with traditional autografts is that they can cause donor site morbidity (Rathbone et al. 2012). Allografts were an earlier alternative for doctors that would remove the nagging problem of donor site morbidity since the ligament is removed from a donor cadaver, but allografts have been known to transmit diseases from cadavers to healthy patients, which is why many patients are hesitant to use them (Chang et al. 2003). In order to circumvent the problems of donor site morbidity, extended recovery periods, and disease transmission, doctors are now looking into tissue-engineered grafts.

Possible Advantages of Tissue-Engineered Grafts

As previously stated, tissue ligament engineering is the creation of an artificial ACL using synthetic materials and stem cells. The reason that this would be beneficial for ACL reconstructive surgery is because the tissue would not be harvested from the patient, so donor site morbidity can be avoided. Also, the tissue will be made of the patient's own cells, so disease transmission is not likely to occur (Patinharayil, 2017). Tissue-engineered grafts could eventually be sturdier than traditional autografts and allografts, so recovery time after ACL reconstructive surgery could be immensely shortened. Since tissue-engineered grafts could offer a solution to many problems traditional grafts cause, many orthopedic doctors are very open to using these grafts in the future when preforming ACL reconstructive surgery (Rathbone et al. 2012). Tissue-engineered grafts might sound great in theory, but there has yet to be a tissue-engineered graft made that has tested successfully on humans.

Disadvantages of Tissue-Engineered Grafts

In the 1970s and 1980s, some synthetic autografts were tested on humans. However, these grafts were very unsuccessful. Almost 80% of these grafts failed in a few years mainly because of wear and tear, tissue rejection, and mechanical problems (Patinharayil, 2017). This failure was disheartening to many doctors, but some used what they learned to improve the previously tested synthetics. Doctors looked to improve the synthetics by changing the materials the synthetics were made of, by testing different types of cells to make the tissue, and by trying to improve the mobility of these tissue-engineered ACL grafts (Yilgor et al. 2012). Even with these changes, many orthopedic surgeons still found problems with tissue-engineered grafts. These grafts are more susceptible to damage than the traditional autografts and allografts, and they are not very long-lasting. Some patients who received tissue-engineered grafts reported graft failures within the first year of using the improved grafts (Dhammi et al. 2015). Along with reduced durability, tissue-engineered grafts could take three to six months to be made before they can be harvested for surgery, while traditional autografts and allografts can be harvested within days to weeks of the ACL injury (Patinharayil, 2017). Therefore, even if recovery time is shortened because of decreased donor site morbidity, ACL patients would still have to wait an unusually long time just to receive the graft they need for surgery.

Future Trends

Decreased durability and mobility, and the extended time it takes to form tissue-engineered grafts are just a few of the major problems associated with artificial ACL grafts. However, new models of tissue-engineered grafts, that have yet to be tested on humans, are being created in order to combat some of these problems. As mentioned earlier, Triton-X is now being used to decrease the graft rejection in patients receiving a tissue-engineered graft, and it can also prevent tunnel widening (Vavken et al.2009). The treatment of tissue-engineered grafts using Triton-X could be the key to making these grafts more durable. Along with Triton-X, orthopedic doctors are also working to develop a better scaffold, or a supportive structure, for the tissue-engineered ACLs to be designed with. One design using a "braid-twist" scaffold is being used to create an artificial ACL graft that is more identical to a patient's actual ACL ligament (Freeman et al. 2006). This upgrade in the design of tissue-engineered grafts could improve mobility after the graft is implanted, make the graft more durable, and also potentially decrease graft rejection.

Summary

Unfortunately, both of these improvements, the "braid-twist" design and the addition of Triton-X, have not been tested on humans yet, so it is difficult to say whether this will ultimately make tissue-engineered grafts the new "gold-standard" when it comes to ACL reconstructive surgery. Therefore, since tissue-engineered grafts are still largely experimental and historically unsuccessful, traditional autografts and allografts should be used and relied on for the time being.

Tissue-Engineered Autograft Implications for Athletes

One of the main reasons orthopedic doctors are more motivated to find an improved graft is because many athletes suffer from ACL injuries. In fact, individuals who participate is sports that involve jumping, pivoting, and cutting are at a much greater risk of rupturing their ACL than non-athletes (Gobbi et al. 2006). Since young athletes are usually eager to return to play, they must undergo ACL surgery to repair the torn ACL, which is usually a time-consuming and grueling task.. Many young athletes deal with nagging soreness and decreased athletic ability which can lead to depression because this extended recovery period causes them to miss out on doing something that they love (Tripp et al. 2007). In order to combat this problem, tissue-engineered grafts are being investigated as an alternative to decrease recovery time for athletes.

Tendonitis and stiffness are common side effects of ACL surgeries when using traditional autografts and allografts, and these problems can make it difficult for athletes to return to the same level of play they had achieved before the ACL injury (Dhammi et al. 2015). Since these problems have been theorized to be eliminated with tissue engineered grafts, many athletes and doctors want to use these grafts for a better and faster recovery. However, even though donor site morbidity is eliminated, other problems such as graft failure and durability keep tissue-engineered grafts from being a better choice for athletes. Instead of athletes, many doctors are now considering tissue-engineered grafts for elderly, less-active patients because tissue-engineered grafts are easily worn-down and damaged (Patinharayil, 2017). Once the problem of graft durability is solved in tissue-engineered grafts, then doctors may consider transitioning them to athletes. Ultimately, if the major problems associated with tissue-engineered grafts are resolved, then these grafts may potentially become the best option for athletes. However, until that day comes, it is probably safest if athletes rely on traditional autografts and allografts when dealing with an ACL injury.

Conclusion

Traditional autografts, such as the patellar tendon and hamstring grafts, and allografts are commonly used in the repair of a ruptured ACL. They are fairly effective, but they also have several side effects such as donor site morbidity, loss of muscle strength, disease transmission, and graft rejection. In order to avoid these problems, orthopedic doctors considered using tissue-engineered grafts, or grafts made of synthetic material and stem cells. Tissue-engineered grafts would not cause problems like donor site morbidity or disease transmission, but they have other major flaws that keep them from currently being better than traditional autografts and allografts. Tissue-engineered grafts take a while to be formed, and they are also less durable. Since these grafts are frailer, they are more prone to failure. Presently, orthopedic doctors are working on ways to improve tissue-engineered grafts so that they are sturdier, but these improvements have yet to be tested on humans. While some doctors are optimistic, as of right now, it is impossible to say whether tissue-engineered grafts are better than traditional autografts and allografts. Until the major problems with tissue-engineered grafts are fixed and successfully tested, then ACL patients, especially athletes, should stick to using traditional autografts and allografts.

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References

Dhammi, I. K., Rehan-Ul-Haq, & Kumar, S. (2015). Graft choices for anterior cruciate ligament reconstruction. Indian journal of orthopaedics, 49(2), 127-8.

Clatworthy, M. G., Annear, P., Bulow, J. U., & Bartlett, R. J. (1999). Tunnel widening in anterior cruciate ligament reconstruction: a prospective evaluation of hamstring and patella tendon grafts. Knee Surgery, Sports Traumatology, Arthroscopy, 7(3), 138-145.

Gobbi, A., & Francisco, R. (2006). Factors affecting return to sports after anterior cruciate ligament reconstruction with patellar tendon and hamstring graft: a prospective clinical investigation. Knee Surgery, Sports Traumatology, Arthroscopy, 14(10), 1021-1028.

Hiemstra, L. A., Webber, S., Macdonald, P. B., & Kriellaars, D. J. (2000). Knee strength deficits after hamstring tendon and patellar tendon anterior cruciate ligament reconstruction. Medicine & Science in Sports & Exercise, 32(8), 1472-1479.

Srinivas, D. K., Kanthila, M., Saya, R. P., & Vidyasagar, J. (2016). Femoral and Tibial Tunnel Widening following Anterior Cruciate Ligament Reconstruction using Various Modalities of Fixation: A Prospective Observational Study. Journal of clinical and diagnostic research : JCDR, 10(11), RC09-RC11.

Chang, S. K., Egami, D. K., Shaieb, M. D., Kan, D. M., & Richardson, A. B. (2003). Anterior cruciate ligament reconstruction: allograft versus autograft. Arthroscopy: The journal of Arthroscopic & Related Surgery, 19(5), 453-462.

Cole, D. W., Ginn, T. A., Chen, G. J., Smith, B. P., Curl, W. W., Martin, D. F., & Poehling, G. G. (2005). Cost comparison of anterior cruciate ligament reconstruction: autograft versus allograft. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 21(7), 786-790.

Rathbone, S., Maffulli, N., & Cartmell, S. H. (2012). Most British surgeons would consider using a tissue-engineered anterior cruciate ligament: a questionnaire study. Stem cells international, 2012.

Vavken, P., Joshi, S., & Murray, M. M. (2009). TRITON-X is most effective among three decellularization agents for ACL tissue engineering. Journal of orthopaedic research, 27(12), 1612-1618.

Nau, T., & Teuschl, A. (2015). Regeneration of the anterior cruciate ligament: Current strategies in tissue engineering. World journal of orthopedics, 6(1), 127-36. doi:10.5312/wjo.v6.i1.127

Yates, E. W., Rupani, A., Foley, G. T., Khan, W. S., Cartmell, S., & Anand, S. J. (2011). Ligament tissue engineering and its potential role in anterior cruciate ligament reconstruction. Stem cells international, 2012, 438125.

Patinharayil G. (2017). Future trends in ACL rupture management. Journal of orthopaedics, 14(1), A1-A4. doi:10.1016/j.jor.2017.01.004

Yilgor, C., Yilgor Huri, P., & Huri, G. (2012). Tissue engineering strategies in ligament regeneration. Stem cells international, 2012.

Laurencin, C. T., Ambrosio, A. M. A., Borden, M. D., & Cooper Jr, J. A. (1999). Tissue engineering: orthopedic applications. Annual review of biomedical engineering, 1(1), 19-46.

Freeman, J. W., Woods, M. D., & Laurencin, C. T. (2006). Tissue engineering of the anterior cruciate ligament using a braid-twist scaffold design. Journal of biomechanics, 40(9), 2029-36.

Tripp, D. A., Stanish, W., Ebel-Lam, A., Brewer, B. W., & Birchard, J. (2007). Fear of reinjury, negative affect, and catastrophizing predicting return to sport in recreational athletes with anterior cruciate ligament injuries at 1 year postsurgery. Rehabilitation psychology, 52(1), 74.