

## Review

# Future perspectives in synthetic grafts used in anterior cruciate ligament reconstruction

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### Abstract

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It is already known that the lesion of the Anterior Cruciate Ligament (ACL) is one of the most frequent knee pathologies, especially in professional sportsmen, but also for the active average-aged population. ACL surgical reconstruction is one of the most documented and common intervention in sport traumatology. The consequence of an ACL lesion is the appearance of anterior-posterior laxity, which leads to an unstable knee predisposed to the appearance of associated lesions and a much faster development of a degenerative disease. That is why in complete lesions of the ACL, the chosen therapeutic attitude is the surgical reconstruction using biological grafts (autograft or allograft) or artificial grafts made from different materials. The limits imposed by autografts and allografts in ACL reconstruction together with the scientific progress made in materials science and biology have conducted a lot of interest for developing systems and materials for anterior cruciate ligament replacement or reconstruction. This review has the purpose to synthesize the important steps taken in the development of polymer-based materials for ACL, their advantages and disadvantages and the results of different *in vitro* and *in vivo* tests. Until now, there is none successfully polymer system for ligament reconstruction implanted in humans. The developing domain of synthetic polymers for anterior cruciate ligament reconstruction still has a lot of potential. In addition, lots of nanostructured materials, made of nanofibers or in the form of ceramic/polymeric nanocomposites, are getting interest of several studies due to their potential use as engineered scaffolds that mimic the native surface composite of cells, increasing the chances for tissue regeneration. Here, we review the last 20 years of literature in order to obtain a good understanding on the use of synthetic grafts made by nano- and polymeric materials for ACL reconstruction, and to trace perspectives on the future development of the field

**Keywords:** Anterior Cruciate Ligament, Grafts, Reconstruction, Knee, Sport Injury

## INTRODUCTION

Soft fibrous tissues, referring to ligaments, connect bone to bone within joints and have a very important role in joint stability especially in load bearing (Amis and

Dawkins, 1991). Ligament tears are a very challenging problem to resolve due to slow or none regeneration rate of ligament tissue. Soft connective tissues such as

tendons and ligaments are typical examples of fiber-reinforced composite materials. They have a very complex hierarchical architecture, responsible for their unique mechanical properties. The most often ligament lesion is the ACL, with over 200,000 reconstructive surgeries only in the US in 2002, covered by expenses of over 5 billion dollars; it is also the most studied ligament and the methods of its reconstruction (Vunjak-Novakovic et al., 2004; Fetto and Marshall, 1980; Pennisi, 2002). An important issue regarding the ACL is the fact that it does not primarily heal, being poorly vascularized compared to other human ligaments (Lu et al., 2005; Bray et al., 2002). Injuries of the ACL cause joint instability, leading to the secondary injury of other intraarticular elements causing degenerative degradation of the knee and a poor life quality for the patient. Several nonsurgical and surgical methods and also different types of grafts have been proposed for the treatment of ACL lesions and deficient knee, but there are controversies about the best procedure. Autografts and allografts were the main graft options for ACL reconstruction. Autografts have short signs such as graft length or diameter, and morbidity of the donor site, while allografts have allogeneic problems, insufficient graft supply, infection risk and disease transmission, difficulties in sterilization, high costs.

Over the past decades, were many debates over what is better for the patient to use, auto or allografts for ACL reconstruction. All these discussions have led to a new branch of development in tissue engineering and polymer biomedical application that includes synthetic implants and biosensors (Ahuja et al., 2007).

Different procedures and various materials have been used over the years and have contributed to the delivery of artificial ligaments as a therapeutic option in knee surgery. However, most of the artificial grafts have been characterized by high rates of failure

To get to a successfully synthetic graft designed from polymer biomaterials, must achieve similar mechanical properties for their intended use, not to induce an inflammatory response, not to release toxic degradation products and to have a degradation time almost like to their function (Lloyd, 2002). Yilgor and colab have recently published a review on tissue engineering strategies for ligament regeneration where they summarize current strategies of the use of scaffolds and bioreactors in tissue engineering, as well as the advances in growth factor and cell therapy in this field (Yilgor et al., 2012).

Nanoscience and nanotechnology are relatively new fields of human knowledge, where interdisciplinary physicists, chemists, biologists, engineers, doctors, and toxicologists, collaborate in the pursuit of solutions for several relevant and actual topics (energy, water, health, sustainability, among many others) (Mendez-Rojas et al., 2014).

The use of new polymeric materials like the nanofibrous materials for regenerative medical procedu-

res, with the intention of regenerate or replace damaged tissues, is an emerging field of biomedicine where an interdisciplinary approach from physics, materials science, medicine, biology, biomedical engineering among several other disciplines converge. Optimization of cell-biomaterial interaction, mimicking the natural biological environment using polymeric or nanostructured scaffolds may be an alternative for future medicine that trends to use more and more regenerative techniques and procedures.

The objective of this review is to show the evolution of polymeric and nano-materials as well as the emerging approaches of the existing materials (polymeric or nano) for anterior cruciate ligament reconstruction.

### Biological grafts

There are three methods for reconstruction or replacing the ruptured ligaments using grafts from living organisms: autografts (Weitzel et al.), allografts (Ambrosio et al., 2010) and xenografts (Woo and Buckwalter, 1988). In current clinical practice, autografts (bone-patellar bone grafts, hamstring or quadriceps tendon) are the most popular grafts used in ACL reconstruction (Li et al., 2012). Autografts present several drawbacks like donor-site morbidity (leading to pain, tendonitis and seldom to patellar fracture), longer recovery times and the requirement of supplementary harvesting procedure (Guarino et al., 2007). Moreover, recurrent injury or failure of the reconstruction do not benefit of the same availability of autologous tissue for surgeries (Cooper et al., 2005)]. Allografts reduce the surgery and recovery time, avoids the donor site morbidity and decreases the postoperative pain. However, in the case of allografts there is a limited tissue supply, a slow biological incorporation and a risk for spread diseases (Kew et al., 2011). There are also some reviews regarding autografts and allografts (Li et al., 2012; Claes et al., 2011; Nandra et al., 2013; Nandra et al., 2013). Kaeding et al. affirmed that there were no significant differences regarding the graft failure rate, postoperative laxity of patient reported outcome scores when comparing ACL reconstruction with autografts or no irradiated allografts. Hu et al. (2013) revealed another review comparing allografts and autografts, this time for patellar bone-tendon-bone graft, and that they couldn't conclude which was the best for ACL reconstruction. Mulford et al.[23] published a systematic review only about quadriceps autografts. Dhawan et al. (2014) reported a review regarding hamstring autografts diameter dimension and their influence on the failure rates.

About xenografts there are only a few studies published in the last years (Stone et al., 2007; Pan et al., 2009; Stone et al., 2007). Stone et al. used transplanted porcine patellar tendon treated with  $\alpha$ -galactosidase to

eliminate  $\alpha$ -gal epitopes and with glutaraldehyde for moderate cross-linking of collagen fibers to replace ruptured ACL in patients. After two years, five of six implants were still in place. They concluded that this kind of porcine implant might be an option. Furthermore, the use of pure xenogenous bovine platelet gel on an artificial tendon was explored to assess their effectiveness for healing and regeneration in a murine model (Oryan et al., 2014). The bovine platelet gel increased cell proliferation and viability (*in vitro*) and showed enhanced cell distribution, proliferation and differentiation, contributing to graft degradation and facilitating the incorporation of the regenerated tissue. In addition, it presented higher mechanical strength due to collagen fibril's better physical properties (density, differentiation, distribution, number), with lower trend for muscle fibrosis and atrophy. In 2011, Chen and colab. explored the autologous tenocyte therapy (ATT) for treatment of tendinosis in a collagenase-induced rabbit Achilles tendinopathy model. Autologous tenocytes were obtained from tendon and peritendineum tissue, and labeled with super paramagnetic iron oxide nanoparticles (Feridex) (Chen et al., 2011). Analysis by histology and immunostaining showed that tenocytes were integrated into the tendon matrix and indicated that the ATT improved collagen expression and tendon regeneration.

### Artificial devices

Another step further in developing ACL injury treatments was taken in the early 1970's, with the FDA approval of the first ACL prosthesis introduced to the market, Proplast from VitelInc, (Petrigliano et al., 2006). In the next years other synthetic grafts were developed: Dacron, GORE-TEX, Leeds-Keio ligaments, Kennedy Ligament Augmentation Device (LAD), ABC Surgicraft, Ligament Advanced Reinforcement System (LARS) (Legnani et al., 2010).

*Dacron ligament* approved in 1989 by the FDA was initially used for acromio-clavicular joint injuries and in ligament reconstructions. This synthetic graft is made from a multilayer of polyethylene terephthalate and polyester with a woven structure from ten yarns and one multifilament transversal yarn, at which were added an external envelope for better tissue incorporation and a central filament for mechanical support. The reported results of this synthetic graft were not satisfactory and in 1994 Striker withdrawn the product from the market 31. (Legnani et al., 2010; Laflamme et al., 2013; Ventura et al., 2010; Maletius and Gillquist, 1997; Barrett et al., 1993).

*ABC Surgicraft ligament* was obtained in 1985 and it is made up from mixture of multiply braided carbon and PET fibers (Legnani et al., 2010; Laflamme et al., 2013). Although its utilization had promising results, afterwards there were several reports about a progressive decrease

of stability, implant degradation due to abrasion and the appearance of inflammatory reactions (Petrou et al., 2006; Mowbray et al., 1997; Jadeja et al., 2007).

The FDA approved *Gore-Tex* ligament in 1986 and it is made of continuous multifilament yarns of tightly braided micro porous polytetrafluoroethylene (Legnani et al., 2010; Laflamme et al., 2013). These kind of grafts have an ultimate strength that is twice the human ACL and a high density, reasons that led to the believe that *Gore-Tex* might be a very good alternative for ACL reconstruction (Bolton and Bruchma, 1983). Due to ruptures of the prosthesis, infections and associated inflammatory responses, this graft was withdrawn from the market in 1993 (Bowyer and Matthews, 1991; Paulos et al., 1992; Rubenstein et al., 1998; Roolker et al., 2000; Matsumoto and Fujikawa, 2001).

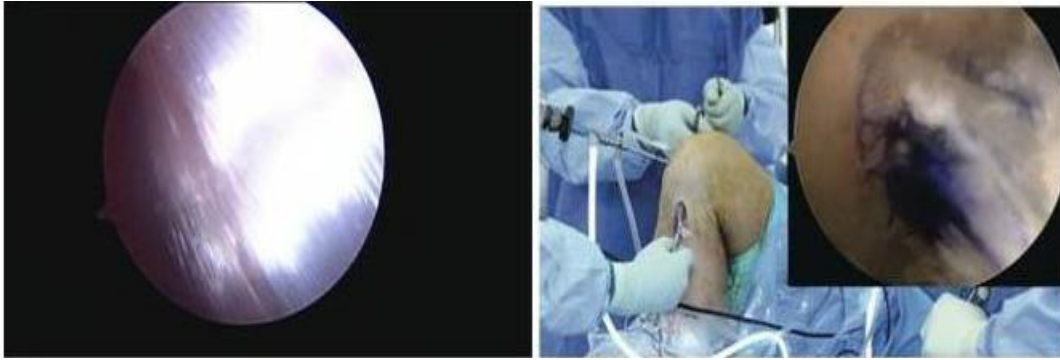
In 1982, the collaboration between University of Leeds and Keio University led to the development of the *Leeds-Keio ligament* that is made of woven PET fibers (Legnani et al., 2010; Laflamme et al., 2013; Matsumoto and Fujikawa, 2001). It was first proposed as a scaffold supporting collagen production, but it was proven that it is only a prosthetic. On long term Leeds-Keio ligaments do not provide suitable guarantees in ACL reconstruction (Murray and Macnicol, 2004; Schroven et al., 1994; Denti et al., 1995; Marcacci et al., 1996; Fujikawa et al., 2000).

The *Kennedy LAD* was introduced in 1975 and is composed of braided polyethylene. It is designed to be implanted in conjunction with biological grafts (Legnani et al., 2010; Kennedy, 1983). Because this device is associated with inflammatory responses, it is no longer recommended for utilization (Kumar and Maffulli, 1999; Riel, 1998; Barrett and Field, 1993).

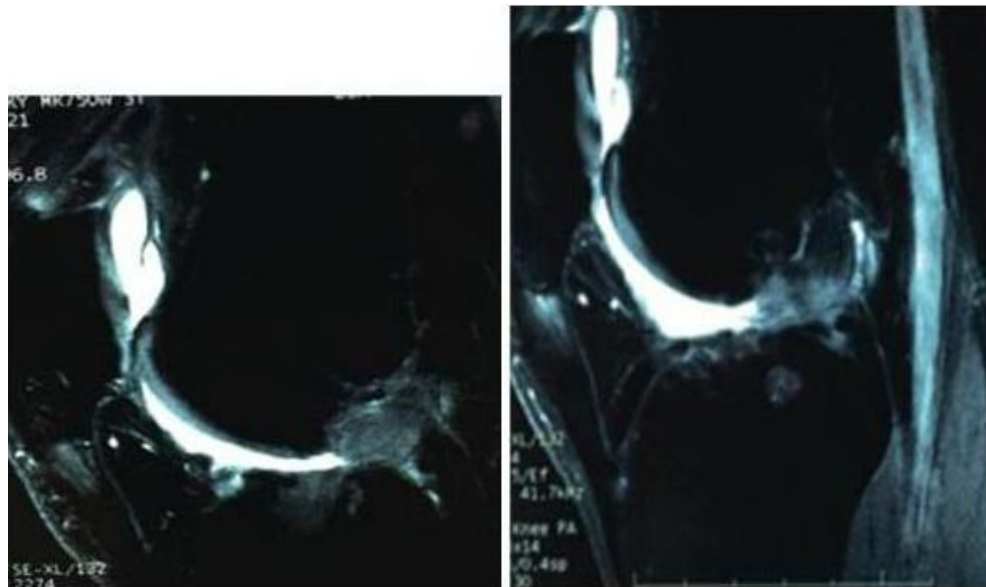
The *LARS ligaments* (Ligament Advanced Reinforcement System) are made of PET fibers with a structure that allow tissue ingrowths, reducing shearing forces and increasing the resistance to wear and tear (Legnani et al., 2010; Laflamme et al., 2013; Shen et al., 2012). The short-term results of this ligament appear good but there is no confirmation of the success of the graft on long-term studies (Newman et al., 2013; Gao et al., 2010; Liu et al., 2010; Li et al., 2012).

The LARS consists of 2 parts, an intraarticular part and a special designed part for bone tunnels (figure 1,2). The medial part of the LARS ligament that remains intra-articular is built of multiple parallel fibers that are rotated at 90-degree angles (Dericks, 1995). This portion is made of 2 longitudinal external rotation fibers without transverse fibers, being designed as an imitation of ACL native structure. The parts that remains in bone tunnels is waved by longitudinal and transverse knitted structure fibers with the aim to avoid ligament deformation. These parts should be aligned perfectly while doing the ACL reconstruction to avoid early graft failures.

The direction of the fibers are modified to be side specific different for left and right knees thus mimicking the 3D cross-sectional anatomy of intraarticular part the



**Figure 1, 2.** Intraoperative image of LARS graft intraarticular and intraosseous



**Figure 3,4.** MRI images with osteoarthritis and LARS graft rupture

native ACL. This is supposed to prevent rotational overlap and points of maximum stress of the synthetic ligament.

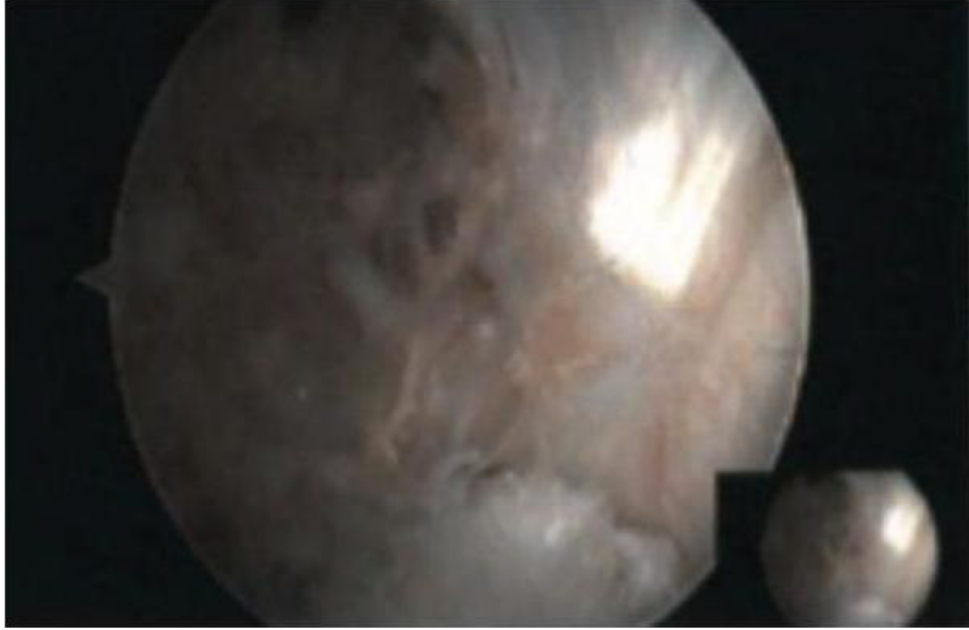
Histopathological studies revealed the cellular ingrowth between the synthetic fibers and that makes LARS acting as a scaffold for new population of fibroblasts (Trieb et al., 2004).

The major disadvantage of the synthetic grafts is their failure over time due to the impossibility of reproducing the mechanical behavior of the native ligaments. These grafts suffer from deformation at the point of maximum stress, consequence of repetitive elongations, weakening due the friction with the bone tunnel, axial splitting, low tissue infiltration and debris creation, which may lead to synovitis. Eventually these implants fail, and certainly, there is a need for more alternatives for ACL reconstruction.

Studying the latest literature, Alberto et al. in their study published in 2014 showed that some patients with failed ACL reconstruction procedures with Polyethylene

terephthalate (PET) synthetic graft (Alberto et al., 2010). Fourteen of such patients underwent revision surgery performed. All these patients had histopathological evidence of intrarticular granulomatous reaction due to PET, and all of them started to develop cartilage damage and osteoarthritis (figure 3,4). Other studies reports disabling synovitis secondary to LARS implantation (Constantine et al., 2002).

So far, dates from literature on LARS remain controversial, and there are no studies to compare the early and longterm outcomes of LARS and allograft/autograft reconstruction. In the authors practice, several cases treated with LARS are symptomatic either because of graft loosening or graft failure (figure 5). Almost all patients who underwent revision surgery, histopathological examination revealed chronic granulomatous inflammation, and patients continued to have symptoms due to inflammatory synovitis and progression of osteoarthritis.



**Figure 5.** Intraoperative image of rupture LARS graft

## RESULTS

After the synthetic grafts, researchers started paying a lot of attention towards the development of scaffolds for ACL reconstruction. Ideally, the scaffold used for the ACL replacement should be biodegradable, but there are certain studies presenting non-degrade. Optimal structural scaffolds for ACL reconstruction should be biocompatible, biodegradable as to allow tissue ingrowth and regeneration of the new ligament, and maintain comparable mechanical strengths to the native ACL. Among the synthetic polymers mentioned in the literature as potential scaffolds for ligament reconstruction there is: collagen, poly-L-lactic acid (PLLA) or poly-L-lactide (PLL), poly-(L-lactide-co-D,L-lactide) (PLDLA), Polyglycolic acid (PGA), poly (D,L-lactide-co-glycolide) (PLGA), polycaprolactone (PCL), poly(desaminotyrosyl-tyrosine dodecyl dodecanedioate) p(DTD DD), poly (desaminotyrosyl-tyrosine dodecyl ethyl ester carbonate) p(DTE carbonate) (Leong et al., 2014), silk, cellulose and alginate.

## CONCLUSIONS

The study and analysis of failures in artificial ligament history has put the basis for future research and studies on finding a synthetic substitute with the best physical and chemical properties (Weitzel et al., 2002). There is still a big amount of research to be done in order to achieve a long lasting successful polymer based scaffold, but the rapid advancements in the field of biology, material science; synthesizing and characterizing

techniques will catalyze the “research process”, but still the development of ideal synthetic scaffold for the ACL reconstruction is a difficult task to achieve. Research in the field of artificial grafts shows that biocompatibility (the degree of polymerization, reduced water adsorption, the absence of soluble additives, chemical stability, the presence of pore for ingrowth of fibroblasts) is the final feature required for these materials; on the other hand, the mechanical characteristics (elongation, tensile strength, stiffness, torsion and abrasion resistance) should be more similar to those of the natural ligament. In addition, the mechanical properties of the scaffold should be similar to those of the native ligament and the degradation products should not produce an immune response. The actual and future advances in materials science, nanotechnology, molecular biology, biomedicine, tissue engineering, along with other fields such as biomedical engineering and robotics, may allow physicians and their interdisciplinary group of work to restore injured or damaged tissues and ligaments more successfully and with better improvement of their clinical outcomes. With constant progress, tissue engineering should provide a functional and biological graft capable of promoting a continuous remodeling of tissues. Despite many efforts and numerous experimental studies, it has been found that each material has several drawbacks, and research to find the ideal replacement, mimicking natural human tissue, is underway.

## Conflict of Interest

No conflict of interests is present.

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