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"Biological failure" of the anterior cruciate ligament graft

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Abstract Anterior cruciate ligament (ACL) reconstruction has the best chance for success when the graft undergoes extensive biologic remodeling and incorporation after implantation. There are many factors that can lead to graft failure and possible revision surgery. These include patient selection; surgical technique such as graft placement and tensioning; the use of allograft versus autograft; mechanical factors such as secondary restraint laxity; lack of a correct, carefully controlled post-operative rehabilitation program; and biological factors. When a patient presents with knee instability following ligament reconstruction and there is no history of a new trauma or identifiable technical error, biological failure should be considered. However, the biologic response of the grafted tissue is closely linked to the mechanical and biochemical environment into which the graft is placed. Thus, the "biological failure" of the ACL graft is a complex pathological entity whose cause is not fully understood. Failure may be initiated by early extensive graft necrosis, disturbances in revascularization, problems in cell repopulation and proliferation, and as well difficulties in the ligamentization process. However, further study of the biological characterization of a failed graft placed in a correct mechanical environment is warranted.

Keywords ACL · Biological failure · Ligament biology · Review

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Introduction

In the past decades major improvements have been made in anterior cruciate ligament (ACL) reconstructive surgery, thus surgical reconstruction is now widely accepted as the treatment of choice for individuals with functional instability due to an ACL-deficient knee [1]. Nonetheless, 0.7–10% of patients develop graft failure with recurrent instability [2–6] and may then be candidates for revision ACL reconstruction.

Failure is likely to be considered when a patient reports functional instability with sports or activities of daily living, a decreased frequency or level of athletic activity with respect to pre-injury status, increased pain, loss of motion, recurrent episodes of giving way, increased pathologic anterior laxity on physical examination with a positive Lachman or pivot shift test, and greater than 5 mm side-to-side difference on arthrometric testing [7]. The University of Pittsburgh group [6] classified the mechanisms of ACL graft failure as related to (a) surgical technique; (b) graft incorporation; and (c) trauma (Table 1). In addition, individual patient factors such as healing potential and compliance undoubtedly play a role in graft failure.

Technical failure is frequently implicated in revision cases, up to 77% in one series [8]. Specific reasons for technical failure include non-anatomic tibial and/or femoral tunnel placement; inadequate notchplasty leading to impingement; improper graft tensioning; graft fixation failure; choice and cross sectional area of the graft tissue; error in graft selection between autograft, allograft and occasionally synthetic graft; and laxity of the secondary restraints. Traumatic failure may occur shortly after the initial surgery, before graft incorporation, due to an overly aggressive physical therapy program during the early rehabilitation period. Or may happen later in cases of traumatic re-rupture, often in athletic individuals.

Table 1 University of Pittsburgh classification for mechanisms of ACL graft failure

A. Surgical technique
 1. Technical errors
  Tunnel location
  Graft impingement
  Graft tension
  Graft fixation
 2. Mechanical/biomechanical factors
  Graft strength (size, hamstring versus BPTB, irradiation)
  Synthetic graft
 3. Secondary stabilizers
  Combined ligament involvement
  Meniscal/articular cartilage loss
B. Failure of graft incorporation
 1. Avascularity
 2. Immunology
 3. Stress shielding
C. Trauma
 1. Traumatic re-injury
 2. Aggressive rehabilitation

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Failure of graft incorporation and ligamentization (as described by Amiel et al. [13]), is commonly referred to as "biological failure" of the ACL graft. It is a complex entity related to problems in the biological processes that directly interact with biomechanical factors to transform the graft into a newly functional ACL [9]. Indeed most grafts used to substitute for a deficient ACL, whether they be allograft or autograft tendon, are histologically and biomechanically different from the native ACL. Tendons consist of 30% collagen and 2% elastin embedded in an extracellular matrix containing 68% water. Collagen, synthesized by fibroblasts, forms 70% of the dry weight of a tendon and has a breaking point similar to that of steel. Elastin contributes to the tendon's flexibility. The ground substance is necessary for the aggregation of collagenous proteins into a fibrillar. Fibroblasts are long, tapered cells often found among collagen bundles. They are seen as thin flat nuclei, and are motile and highly proliferative. They form collagen, elastin, and ground matrix, and increase in number during wound healing [10]. Ligaments are fibrous connective tissues comprised of ground substance (water and proteoglycans), cells (primarily fibroblasts), and fibrous elements (collagen, elastin, and reticulin). Ligaments are composed mostly of water (60–80% net weight) and type I collagen (65–80% dry weight). The ground substance (approximately 1% dry weight) consists primarily of proteoglycans, which serve to hold water. Ligaments also contain small amounts of actin, fibronectin, and other substances of unknown significance, and are relatively avascular with low blood flow [11].

Compared to tendons, ligaments are metabolically more active, have plumper fibroblast nuclei, higher DNA content (more cells), more type III collagen, more proteoglycans, less total collagen, and a different proportion of reducible intermolecular collagen bonds [12]. In a rabbit model, Amiel et al. demonstrated that autografts undergo a ligamentization process, defined as a transition of the biomechanical and histologic parameters of the graft from tendinous to ligamentous in appearance. This remodeling of the graft tissue occurs in the new intra-articular environment specific to the native ACL [13], and while it is complex, ingenious and leads to a fully incorporated graft, it does not result in a duplication of the native ACL.

Animal and human models have shown the stages of this ligamentization process, which includes avascular necrosis, revascularization, cellular repopulation, collagen remodeling, and maturation [14, 15]. In the context of the current literature, this article discusses the "biological failure" of the ACL graft, specifically its definition, possible causes and its consequences. The objective is to summarize what is known, what is not known, and the possibilities for further research.

Definition

As a general concept, failure of an ACL graft should be considered when restoration of stability and return to activity have not been achieved in a patient who has undergone ACL reconstruction. Without a history of a new trauma, and in the presence of a knee without laxity of the secondary restraints and no detectable technical errors, one can entertain the diagnosis of "biological failure". This definition lacks precision, is not very satisfying, and is more a diagnosis established by exclusion of other causes of failure.

Biological failure can also be defined as a failure in the completion of the ligamentization process, leading to an atonic, disorganized, and non-viable graft (Fig. 1). Marumo et al. [16] explained the changes that might occur in the collagen concentrations and biochemical profiles of the ACL graft. As the center of the transplanted tissue is initially avascular with relatively low numbers of viable cells, collagen synthesis cannot be very active in the early postoperative months, even though vascular invasion from the surface of the graft occurs within 3 to 8 weeks after the reconstruction and is followed by a repopulation phase [17–19]. Increased revascularization, release of growth factors by viable cells that enter the graft tissue through the newly formed vessels, and mechanical forces all stimulate collagen production. Collagen content increases with time and may become even higher than in the native ACL, probably because of a higher cell density and collagen over-expression during the first year after the initial surgery. The conversion

Fig. 1 Loose, atone and avascular ACL hamstring graft 2 years post-implantation. Despite a large volume of collagen, the graft is incompetent and disorganized
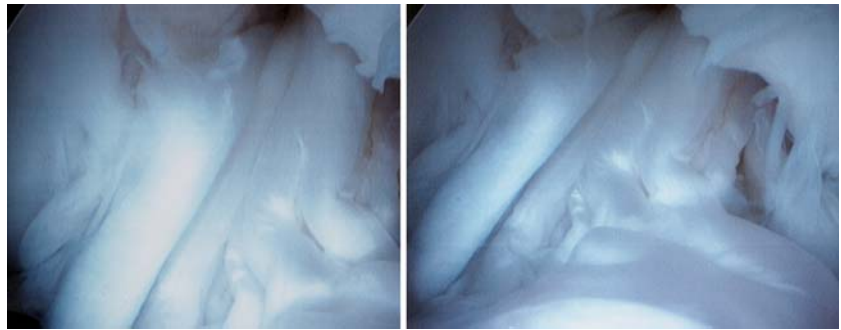
of collagen cross-linkage from reducible (tendons) into non-reducible (ligaments) occurs simultaneously with collagen synthesis and mechanical stress, as well as with other intra-articular factors that might contribute to this re-arrangement (and thus ligamentization) [16]. In order to determine the histology of ACL grafts that failed to incorporate, Alm et al. [20] performed biopsies on 22 patients who were 3 months to 5 1/2 years following patellar tendon autograft ACL reconstruction. They found central necrosis of the grafts and complete vascularization by 8 weeks. In those with intact grafts, the histology resembled a normal ACL except for continued hypercellularity. In those grafts that were ruptured or clinically lax, histology revealed disintegration and fragmentation of the collagen with gross disorganization of the graft component parts [20, 21]. Malinin et al. also found that lax grafts remained histologically disorganized for up to 3 years post-implantation [22].

Thus, a microscopic definition of biological failure appears more reliable and appropriate. If greater than 1 year post-implantation a lax graft shows extensive necrosis, hypocellularity, poor vascularization, disintegration, fragmentation, and disorganization of the collagen, it should be considered as biologically failed.

The biologic response of the grafted collagenous tissue is intimately linked to the biomechanical and biochemical environment into which the graft is placed [23]. As previously mentioned, "biological failure" is a concept still under investigation and should remain a diagnosis of exclusion. The following section details the biological mechanisms that might lead to failure of graft incorporation. These include graft necrosis, revascularization, cell repopulation, collagen remodeling and ligamentization, immunologic response, and stress shielding.

Biological factors

Graft necrosis

In the first 3–4 weeks following implantation most authors agree that the graft undergoes avascular necrosis mainly in its central portion [13, 24–26]. As part of this necrotic

process, several cytokines are released and initiate the cascade of growth factors that guide the different incorporation steps such as revascularization, cell migration and proliferation [27, 28]. Extended necrosis could result due to the major biological changes occurring within the intra-articular environment after the operation. It has been shown [29, 30] that levels of matrix-metalloproteinase (MMP3), tissue inhibitor of metalloproteinase (TIMP)-1, interleukin-6 and 8 (IL-6, IL-8), tumor necrosis factor alpha (TNF-a), interleukine-1 (IL-1), and low density of interleukin-1 receptor antagonist (IRAP) are increased in the ACL-injured knee, and the same response may occur after ACL reconstruction. Such changes may create an antagonistic environment for the newly grafted tissue and result in extended necrosis, collagen disturbance (disintegration, fragmentation, disorganization), myxoid degeneration and finally interfering with the process of revascularization. However, clinical observation of failed grafts rarely shows complete disappearance of the grafted tissue, implying that necrosis is a limited process in most cases.

Revascularization

Since the ACL graft undergoes necrosis following implantation [24], adequate revascularization is critical for successful graft incorporation by allowing cellular repopulation and subsequent matrix remodeling. Indeed, early revascularization of the ACL graft brings in viable cells which release growth factors and produce collagen typically characteristic of ligamentous tissue. At 3 weeks, post-operative grafts show early revascularization and are well perfused by 6–8 weeks. Graft revascularization has been shown to predominantly originate from the infrapatellar fat pad distally and from the posterior synovial tissues proximally. Consequently, during notch preparation, one must avoid aggressive shaving of the fat pad and the posterior synovial tissue, to enhance the revascularization process [14, 31].

The major causes for impairment of revascularization include: (a) Over-tensioning of the ACL graft, which induces focal myxoid degeneration and marked changes in its histologic appearance. This suggests that graft should be

fixed under optimal preload [32]; (b) Patients habits, including smoking, cocaine consumption, or systemic diseases such as diabetes. Cocaine-associated cerebral vasculitis has been described, and biopsies of brain tissue reveal a non-necrotizing leukocytoplastic angiitis of the small vessels [33]. This same mechanism may interfere with revascularization of the ACL graft leading to the cases of biological failure we have observed among cocaine abusers (Fig. 2). In diabetic patients, microangiopathies may lead to the same phenomenon. In smokers, nicotine is a potent vasoconstrictor [34] and inhaled carbon monoxide reduces tissue oxygenation and impairs the microcirculation within healing soft tissue and bone [35, 36]. While these patient factors may theoretically contribute to the failure of graft revascularization and incorporation, Karim et al. [37] did not report on specific biological failure among smokers; (c) Choice of graft, whereby revascularization and cell repopulation have been demonstrated to occur earlier with autograft versus allograft [15], and allografts have been shown to be revascularized and remodeled superficially with incomplete healing in the central portion of the graft [38]; (d) Hypoxia during the period of avascular necrosis. It has been shown that VEGF expression is up-regulated during the early phase following graft implantation [39], and in situations of extended graft necrosis and destruction of engrafted cells the missing trigger for angiogenesis, and the resulting decreased expression of VEGF, may cause failure of the revascularization process.

Cellular repopulation and proliferation

Cellular repopulation with mesenchymal stem cells and regenerative fibroblasts, as well as revascularization, have been shown to be completed 12 weeks after surgery. This correlates with the presence of PDGF-AA, PDGF-BB and

Fig. 2 Anterior cruciate ligament (ACL) graft 1 year post-implantation in a professional football player abusing of drugs (cocaine, amphetamine, methadone). **a** T1-MRI view in the ACL plane. **b** Coronal T2 MRI view. **c** Arthroscopic view of the loose and atone graft. **d** The graft is disorganized. **e** Definitively loose at palpation. **f** The graft has been cut transversally allowing for the distinction of superficial layers with vasculature and central zone (*arrows*) avascular and necrotic
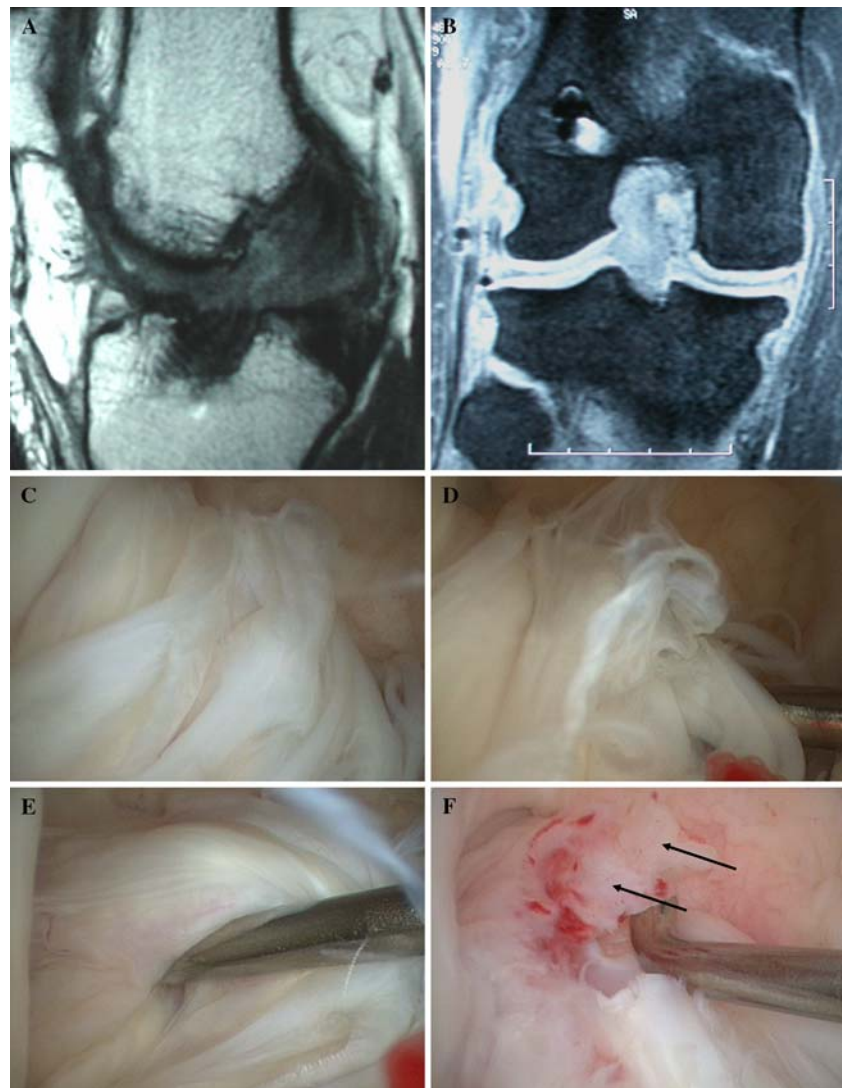
TGF-β1 in the reconstructed graft and these growth factors are not present in the native ACL [28]. Further studies are needed to clarify the exact role of these growth factors but it can be assumed that a lack of them could lead to biological failure. A deficient revascularization process results in a lack of available oxygen for cells, thus limiting growth factor production. Since these growth factors have an autocrine and paracrine action their decrease will result in a diminution of cell proliferation as has already been shown in vitro [40–43]. This phenomenon will clearly interfere with the ligamentization process that follows.

Collagen remodeling and Ligamentization

For many years, it has been known that collagen fibrils in the reconstructed ligament are differently organized than those of the native ACL [44], having a unimodal, small diameter collagen-fibril diameter profile [45, 46] and the remodeling process never results in exact reproduction of the original ligament organization. However, this ligamentization process is crucial to restore the mechanical properties of the graft. Total collagen content and the non-reducible/reducible crosslink ratio increase within one year after graft implantation [16]. Collagen production requires sufficient revascularization, release of growth factors by viable cells, and adequate mechanical forces. Obviously, the failure of one of these parameters impairs the entire process. The conversion of collagen cross-links from reducible into non-reducible occurs simultaneously with collagen synthesis and mechanical stress [16]. As previously mentioned the mechanical environment of the graft directly influences these changes, and this depends more upon surgical technique and the rehabilitation regimen than biology. Tunnel placement is currently thought to be the most critical factor in determining ACL reconstruction success or failure, because tunnel placement directly affects the mechanical properties of the graft and therefore directly affects the ligamentization process of the healing graft. For example, a femoral tunnel that is positioned too anterior, results in a lack of the parallel alignment of collagen fibers and leads to collagen fiber fragmentation [21]. Thus, loss in graft mechanical properties may be related to non-physiologic graft position and tension, instead of being the consequence of the remodeling process. It appears clear that rather than being a biological failure, this represents a technical failure [47].

As concerns ligamentization, we observed two cases of extensive hypertrophy of the grafted tissue, and one case of bone metaplasia within the graft itself (Fig. 3). Despite the increased content of tissue, theses grafts were loose and atonic with a decrease in cell density and highly

Fig. 3 BPTB ACL graft containing ossification. Bone can be seen in the mid-substance of the implanted ACL graft (*arrow*) and in its distal portion 3 years after the surgery

disorganized collagen bundles. We have no explanation for this phenomenon.

Immunology

It has been demonstrated that allografts harvested under sterile conditions (non-irradiated, non-gas sterilized) and fresh-frozen before implantation often lead to bone resorption and tunnel enlargement [48]. Tunnel enlargement is a failure of graft incorporation. While the incidence of tunnel enlargement is significantly higher in patients following allograft as compared to autograft, the explanation is unknown, but may be due to immunologic reaction enhanced by the allograft [48]. Indeed, Harner et al. [49] found a significant donor-specific immune response in patients who had undergone fresh frozen bone-patellar tendon-bone allograft ACL reconstruction, with the expression of IgG antibody to donor human leukocyte antigen-class I antigen. Arnoczky et al. [31] reported reduced graft antigenicity associated with deep freezing in comparison with the marked rejection and inflammatory response in the fresh specimens. They hypothesized that the freezing process may denature cell surface marker proteins and disrupt cell membranes, thereby reducing antigenicity [31]. Thus, immunologic reactions may explain why the rate of incorporation is dependent upon the type of graft material and the method of fixation. For example, Jackson et al. [47] demonstrated that allografts have a longer and less complete course of incorporation and remodeling when compared with autografts, and that the allografts were shown to be biomechanically inferior to the autografts. This slower histologic incorporation may result in diminished graft function [47]. However, there is

no evidence in the literature that allograft reconstruction leads to a higher rate of biological failure.

Stress shielding

Graft tensioning during surgery and the postoperative rehabilitation program have to be balanced to permit optimal graft healing. It is agreed that the ACL graft is only incorporated in the presence of mechanical loading, but the magnitude of this load has yet to be determined. Shelbourne and Nitz [50] showed that patients who returned quickly to high-risk activities achieved normal function earlier than those who complied with the postoperative regimen. However, patients undergoing aggressive rehabilitation have developed degenerative changes in the reconstructed ligaments [T. Yamagishi et al. (2000), unpublished data], and clinical studies have indicated that an early return to vigorous physical activity may increase the risk of greater knee laxity after ACL reconstruction with either a patellar tendon (BPTB) [51, 52] or hamstring graft (StG) [53]. Yoshiya, et al. [32] showed that long-term knee stability may be dependent on initial tensioning, and that over-tensioning ACL grafts may adversely affect their biologic incorporation, leading to delayed graft incorporation, myxoid degeneration, decreased graft strength, and over-constraining the joint. Beynnon et al. [54] demonstrated during knee flexion intraoperatively that graft elongation values outside the limits of the ACL resulted in a significant increase in anterior laxity at a 5 year follow-up, while grafts with elongation values similar to the normal ACL did not do so.

In summary, the ACL graft heals only if the reconstruction can restore the anatomy of the native ACL and mimic as closely as possible the biomechanical environment of an intact ACL.

Discussion

Biological ACL graft failure is a complex pathological entity not completely understood. Any factors affecting graft revascularization, cellular repopulation, or matrix remodeling can lead to biological failure. However, the biologic response of the grafted collagenous tissue is intimately linked to the biomechanical and biochemical environment into which the graft is placed. Therefore, graft failure may often result from the inability to precisely reproduce physiologic tension and position, and is not a consequence of the remodeling process [23, 47]. Graft incorporation is influenced by many factors, primarily technical and biomechanical, and cannot always be appreciated objectively. It is difficult to appreciate the

concept of genuine biological failure, and the diagnosis of "biological failure of an ACL graft" should be considered more as an exclusion diagnosis rather than a real pathological entity.

Most of our knowledge concerning ACL graft incorporation comes from animal models, but human biopsy studies have shown that there are important differences in graft healing between human and animals. Thus animal data cannot be directly transferred to the human, although they do provide substantial help in understanding the biological processes. Further human studies are needed to clarify this concept of biological ACL graft failure, to understand its pathogenicity, and mainly the ways to prevent and to treat its occurrence. At present, we do know that the biological response of the engrafted tissue is intimately related to the mechanical and biochemical environment into which the graft is placed. The surgeon is directly responsible for the mechanical aspects, and the patient, is responsible for providing the appropriate biochemical environment. Therefore each of these factors must be considered individually in our approach to ACL reconstructive surgery.

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