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Allograft tendons are a safe and effective option for revision ACL reconstruction: a clinical review

V. Condello[1] · U. Zdanowicz[2,3] · Berardo Di Matteo[4,5] · T. Spalding[6] · P. E. Gelber[7,8] · P. Adravanti[9] · P. Heuberer[10] · S. Dimmen[11] · B. Sonnery-Cottet[12] · C. Hulet[13] · M. Bonomo[14] · E. Kon[4,5]

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Abstract

Revision anterior cruciate ligament reconstruction remains a challenge, especially optimising outcome for patients with a compromised knee where previous autogenous tissue has been used for reconstruction. Allograft tissue has become a recognized choice of graft for revision surgery but questions remain over the risks and benefits of such an option. Allograft tendons are a safe and effective option for revision ACL reconstruction with no higher risk of infection and equivalent failure rates compared to autografts provided that the tissue is not irradiated, or any irradiation is minimal. Best scenarios for use of allografts include revision surgery where further use of autografts could lead to high donor site morbidity, complex instability situations where additional structures may need reconstruction, and in those with clinical and radiologic signs of autologous tendon degeneration. A surgeon needs to be able to select the best option for the challenging knee facing revision ACL reconstruction, and in the light of current data, allograft tissue can be considered a suitable option to this purpose. *Level of evidence* IV.

Keywords ACL · Revision · Allograft · Multi-ligament · Arthroscopy · Return to sport · Anterior cruciate ligament

✉ Berardo Di Matteo
berardo.dimatteo@gmail.com

U. Zdanowicz
u.zdanowicz@icloud.com

[1] Department of Orthopaedics, Clinica Humanitas Castelli, Via Mazzini, 11, Bergamo, Italy

[2] Carolina Medical Center, Pory 78, 02-757 Warsaw, Poland

[3] McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, USA

[4] Department of Biomedical Sciences, Humanitas University, Via Manzoni 113, Rozzano, 20089 Milan, Italy

[5] Humanitas Clinical and Research Center, Via Manzoni 56, Rozzano, 20089 Milan, Italy

[6] University Hospitals Coventry and Warwickshire (UHCW), Coventry, UK

[7] Orthopaedic Department, ICATME-Institut Universitari Quirón-Dexeus, Universitat Autònoma Barcelona, Barcelona, Spain

[8] Orthopaedic Department, Hospital de Sant Pau, Universitat Autònoma, Barcelona, Spain

[9] U.O. Ortopedia, Clinica "Città di Parma", Parma, Italy

[10] Herz-Jesu Hospital, Vienna, Austria

[11] Lovisenberg Diaconal Hospital, Lovisenberggt. 17, 0456 Oslo, Norway

[12] Centre Orthopédique Santy, FIFA Medical Centre of Excellence, Groupe Ramsay-Générale de Santé, Hôpital Privé Jean Mermoz, Lyon, France

[13] Department of Orthopaedic Surgery and Traumatology, Unit INSERM COMETE, UMR U1075, Caen University Hospital, Caen, France

[14] Orthopaedic Department, Sacro Cuore-Don Calabria Hospital, Via Don A. Sempreboni, 5, 37024 Negrar, VR, Italy

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Introduction

Although significant advances in anterior cruciate ligament (ACL) reconstructive surgery have been made in the past decade, clinical failure continues to occur, with a reported rate of 2–3% of patients in the first 2 years [58] and up to 25% at a 10-year follow-up [14]. Graft failure is a devastating outcome, making revision ACL reconstruction an important orthopedic procedure to restore joint stability and knee function. Outcomes after revision ACL reconstruction are generally inferior to those after primary ACL reconstruction. Only 43% of patients have been reported to return to their previous activity level, a significantly lower figure than that reported for primary ACL reconstruction [3]. In addition, the failure rate is significantly higher than in primary cases. Although it has been recently reported that graft choice in revision ACL reconstruction has no influence on the rate of return to sport at the pre-injury level, most surgeons still believe that graft choice remains relevant. While autografts are largely the most commonly used grafts in primary ACL surgery, some surgeons prefer to avoid donor site morbidity for a second or third revision. In these cases, allografts become a good alternative, being the selected choice in 20–51% of revision cases [3, 46]. Despite their frequent use, there is not enough information regarding several characteristics of the allografts to include their use in evidence-based recommendations for revision ACL surgeries. Most of the available data on allografts is from experience gained with primary ACL reconstruction. In these primary ACL surgeries, allografts have shown a higher risk of failure than autografts [43], particularly in young, highly active patients. Similarly, the Multicenter ACL Revision Study (MARS) group reported that the use of allografts in ACL revision cases resulted in patients being 2.78 times more likely to sustain a subsequent graft rupture than patients treated with autograft [43]. In this large study, allograft patients also showed inferior functional outcomes. Several specific details of allografts in revision ACL cases are missing in the literature, whereas few data are available regarding the type of tendons, the most appropriate sterilization and storage methods, surgical techniques and graft preparation, complications, specific rehabilitation and functional outcomes, particularly in comparison with autografts.

The aim of this paper was to perform a comprehensive literature review to provide the state of the art regarding the use of allografts in ACL revision surgeries.

Biology of ACL revision with allograft tendons

Allografts offer the advantages of decreased operative times and solve the problem of limited availability of donor tissue in this type of patient. Possible disadvantages include a risk of disease transmission, immune rejection, delay in the remodeling and prolonged integration process [10].

Despite the wide use, very little is known about the basic science of integration, remodeling and healing of allografts, crucial factors necessary to suggest clinical indications or contraindications. A basic understanding of the biologic process that affects the donor–host interactions and eventual incorporation and remodeling of various allograft tissues, is a fundamental prerequisite for their successful clinical use. Ideally, a graft used for surgical reconstruction should be able to recreate the anatomical and biomechanical properties of the native tissues by guaranteeing safe fixation together with a rapid biological integration, quick recovery time and no donor site morbidity. Compared to autograft, allograft incorporation proceeds with a similar but slower progression [17], with three biological stages: first, an early and acute inflammatory process with ischemic necrosis and no detectable revascularization; then, cell recruitment and chronic inflammation with revascularization, proliferation and collagen remodeling; and finally, a ligamentization phase. In the very early phase, acute inflammatory response occurs: within the forming fibrin clot, platelets aggregate and degranulate, releasing several growth factors. Transforming growth factor-β1 (TGF-β1) attracts neutrophils and monocytes at about 24–48 h after operation [39], inducing them to generate chemokines and additional components of the pro-inflammatory cytokine cascade. After these early events, until the fourth post-operative week, necrosis increases mainly in the centre of the allograft. Graft necrosis leads to a release of growth factors, which stimulate cell migration and proliferation as well as extracellular matrix synthesis and revascularization [70]. Mesenchymal cells, originating from the host synovial fluid or bone marrow, are attracted into the intra-articular portion of the allograft, which act as a type I collagen scaffold [36]. Revascularization starts on the fourth post-operative week [59], progressing predominately from the infra-patellar fat pad distally and from the posterior synovial tissues proximally. Neovascularization is crucial also for the graft-host interface in the bony tunnels, where it is accompanied by recruitment of host-derived cells with cartilaginous morphology. The maturation of the graft-bone interface over time gradually leads to the formation of Sharpey's-like fibers, firmly anchoring the graft to the bone. The process then goes on to restore the four layers that typically compose the ACL-to-bone insertion, i.e., dense connective tissue, fibrocartilage, mineralized fibrocartilage and bone [6, 51]. Between 4 and 12 weeks, a strong proliferation phase is accompanied by changes in the extracellular matrix. Host fibroblasts and synovial cells repopulate the transplanted tendon after donor fibroblast necrosis during the early phase, and remodel the provisional matrix. Increased collagen III

synthesis (with lower mechanical strength than type I collagen), together with the loss of the original large-diameter collagen fibrils in favor of smaller-diameter fibrils may explain the reduced mechanical strength of the graft versus the intact tendon [59]. From week 12 onwards, the allograft tendon continuously remodels towards the morphology and mechanical strength of the intact/original tendon or ligament and reaches its maximum properties at around 1 year. Collagen fibers regain their organization, although the heterogeneous composition of collagen fibers of varying diameter of the intact ACL is only partially restored [1]. Cellularity slowly returns to values of the intact tendon between 3 and 6 months with vessels becoming evenly distributed throughout the entire graft at 12 months [59], although the central portion of the graft remains essentially acellular.

Fresh tendon allografts have been shown to stimulate an immunologic reaction after implantation in the host, with lymphocyte invasion, hyperaemia, and rejection [5] and have, therefore, been abandoned. Freezing the graft alters the major histocompatibility complex and leads to cell death, without altering the structural and mechanical properties. Thus, deep-frozen nonviable grafts are more suitable than fresh tendons because host rejection is a rarity. However, a more occult response in frozen grafts might cause the delayed incorporation and ultimately graft failure.

Many biological issues such as chemical composition, incorporation, remodeling and immune responses are still to be further assessed. It clearly emerges that cell types, growth factors and cytokines are involved in a coordinated manner during the early inflammatory and further remodeling phases. A better understanding of the complex biological events occurring during graft maturation will lead to improved biologically driven strategies for allogeneic implants.

Sterilization and storage

Processing methods for sterilization of allografts prior to their clinical use include cryopreservation, freeze drying, washing, and irradiation, as well as more innovative tissue disinfection and sterilization procedures (Table 1) [18]. Radiation in particular has been shown to diminish mechanical strength of grafts through a direct damage to collagen fibers and extracellular matrix, that ultimately reduce toughness and resistance to failure of the irradiated grafts [29, 33]. Therefore, processing of allografts without gamma radiation, is believed to be advantageous for graft incorporation [63]. In analysis from the Kaiser Permanante registry, Tejwani et al. [62] found an increased revision risk for grafts treated with the BioCleanse Tissue Processing System and for use of irradiation greater than 1.8 Mrad. Other processing methods such as Allowash or AlloTrue did not affect revision rate significantly.

Sun et al. showed in three prospective randomized studies that non-irradiated bone–patellar tendon–bone (BPTB) and hamstring tendon (HAT) allografts compared to autografts did not show a significant higher revision rate or side-to-side

Table 1 Summary of different allograft processing techniques (Modified from Roberson et al. [57])

Process	Company	Primary processing	Irradiation
AlloTrue™	AlloSource (USA)	Antibiotics, alcohol, peroxide, ultrasonification, multiple water rinses	Yes, terminal (dose 1–1.3 Mrad)
Allowash®	LifeNet Health (USA)	Flushing, centrifugation, hypotonic processes, ultrasonification	No
Allowash XG®	LifeNet Health (USA)	Flushing, centrifugation, hypotonic processes, ultrasonification	Yes, terminal (dose < 2.0 Mrad)
ARCTS	American Red Cross Tissue Service	Unknown	Unknown
BioCleanse	Regeneration Technologies Inc	Repeated cycles of pressure and vacuum with detergent and sterilant washes, hydrogen peroxide, isopropyl alcohol, mechanical oscillations, pharmaceutical-grade water washes	No
Clearant	Clearant Inc	Graft freezing with water removal, addition of dimethyl sulfoxide and antioxidants	Yes (dose: 5 Mrad)
CTS	Community Tissue Services	Multiple solution soaks/rinses	Yes
MTF	Musculoskeletal Transplant Foundation	Antibiotic soak, agitation, controlled and purified water rinse	40–65% of grafts, pre-processing (1.2–1.8 Mrad)
Supercritical carbone dioxide	NovaSterilis	Low temperature, low pressure, proprietary sterilization additive	No
Tutoplast	Regeneration Technologies Inc	Ultrasonification, acetone wash, hyperosmotic wash, sodium hydroxide, hydrogen peroxide	Yes, terminal (1.78–2.01 Mrad)

differences of more than 3 mm by KT-2000 arthrometer, whereas allograft irradiated at 2.5 Mrad showed a significantly increased revision rate and knee laxity when measured by the KT-2000 arthrometer, suggesting a potential deleterious effect on the implanted allograft tissue by irradiation [61].

In a recent systematic review, Roberson et al. [57] could not find any significant difference in patient-reported outcomes between different processing techniques except for the Tutoplast process. The clinical failure rate of the Tutoplast process was reported to be 45% at 6 years, whereas for other processing techniques no difference was found (BioCleanse: 5.4%; AlloTrue: 5.7%; MTF: 6.7%).

Irradiation is the only processing method with a reported deleterious effect on allografts. Because it seems that the effect is dose dependent, a threshold below 2 Mrad is considered as low-dose irradiation with minimal effects on biomechanical properties [23, 28].

Although there is a trend towards irradiated allografts because of safety issues, the majority of the companies use a system of pre-processing or terminal low-dose radiation (see Table 1). Nonetheless, surgeons need to be aware of the fact that low-dose irradiation when claimed by companies may not actually be below 2 Mrad. It is crucial for surgeons to have information about the processing of allograft tendons from the specific tissue bank. Processing methods not using irradiation also need to be further assessed since osteoinductivity may be compromised as shown for the BioCleanse processing method. Negative effects on graft incorporation and ligamentization may be possible [42].

Further studies are warranted for novel sterilization processes as Clearant, supercritical carbon dioxide, or E-beam processes to assess failure rates and clinical outcomes. Furthermore, to allow direct comparisons, future studies on ACLR with allografts should clearly specify the source of the graft and the processing techniques.

Timing and treatment plan

Pre-operative planning involving comprehensive clinical and radiological evaluation is the first and most important step to allow an accurate and effective stepwise approach. Patient symptoms should be carefully analysed with particular attention to instability sensation, swelling, locking, stiffness and pain. The medical history will provide the surgeon with information about the previous injury, how it occurred, the post-operative rehab course (unusual rehab, stiffness, early return to activity), the mechanism and timing of re-injury. Key points to be discussed are previous activity level and the patient expectations. It is always necessary to rule out the possibility of an infection and blood tests for inflammatory markers (white blood cell count, C-reactive protein, and erythrocyte sedimentation rate) must be requested. Full detail of the previous surgery must be known as well as the presence of associated lesions and the way in which they have been addressed, along with the type of graft and the type of fixation used.

A careful clinical examination is important to establish the degree of instability and the association of peripheral lesions or rotatory instability [66]. Imaging evaluation should include X-ray, MRI and CT scan. A complete X-ray series should be obtained including weightbearing AP in extension, weightbearing 45° flexed PA, Skyline/Merchant view [54], full-length standing AP view to evaluate the knee alignment, and a lateral view at 30° of flexion and in full extension to analyze tibial slope and previous tunnel placement. The MRI is useful to analyze the status of the graft, cartilage, menisci and the surrounding soft tissues. Measurement of the antero-posterior translation and rotatory laxity is important such as using the PKTD (Porto-knee testing device) during MRI examination. The CT scan with 3d reconstruction is fundamental to proper investigate the tunnel position, the size, possible widening and the presence of hardware. Varus alignment could lead to early medial osteoarthritis and increase the load on the reconstructed ACL, increasing the risk of failure [67]. In those cases, especially when associated with a progressive postero-lateral corner insufficiency, combining ACL reconstruction with high tibial osteotomy (HTO) has shown to be a reliable procedure to improve the function, providing further stability and pain reduction.

Once all the necessary information has been obtained, the surgeon can choose a one- or a two-stage revision, the type of graft and the requirement for associated treatments, such as lateral extra-articular tenodesis or osteotomy. Patients with tunnels in good positions, with limited or no widening, and with easily removable hardware, are candidates for single-stage revision as well as those patients in which previous tunnels are poorly positioned not interfering with the planned new tunnels. A two-stage revision is recommended when the prior tunnels are correctly positioned but significant widening has occurred [19]. It is still debated the amount of the tunnel enlargement which may induce the surgeon for a two-stage procedure. Some authors [56] suggest that, in case of tunnels wider than 16 mm, the best treatment is bone grafting and two-stage reconstruction. If the tunnels are 16 mm or less and the tunnel expansion is localized far away from the point of the graft fixation, a one-stage reconstruction is still the best choice. Other authors consider 12 mm the maximum amount of acceptable tunnel widening for a single-stage ACL revision [11]. There is more consensus to the view that tunnel widening greater than 15 mm need a bone grafting and two-stage procedure, while a tunnel with a diameter less than 10 mm can be used without grafting, allowing a single-stage procedure. Tunnels

between 10 and 15 mm need more careful evaluation and may need bone grafting, depending on the anatomical tunnel position and on their shape which could be irregular, secondary to osteolysis.

Other indications for a two-stage revision are loss of range of motion, and concomitant surgery that would slow down the post-operative recovery.

Surgical technique: single stage vs two stage

Different surgical techniques has been described to deal with ACL revision surgery, but the surgeon should customize the choice to the patient, to the type of trauma and to the grade of knee stability [12, 37].

Two main approaches are described: the single-stage or the two-stage ACL reconstruction. Single-stage revision, which is currently the most common situation in ACL revision surgery, can be performed in a patient with good bone stock, no tunnel widening, no associated injuries (malalignments, meniscal and chondral lesion, unless treated simultaneously), no interference between the new and old tunnels, and no hardware removal problem. Indications for two-stage revision include loss of range of motion (loss of extension greater than 5° or loss of flexion greater than 20°) and arthrofibrosis [11, 16].

The approach should be chosen preoperatively but the surgeon should be ready to change the procedure after arthroscopic evaluation of tunnel placement. The two-stage procedure is performed in 6–9% of all ACL revision cases [11, 48].

Single-stage revision

The patient is placed in the supine position with a tourniquet and a standard arthroscopic set-up. Pinpoint tunnel position is important: knowing previous surgical technique gives some primary indications. Tibial tunnel is often more posterior in transtibial technique while femoral tunnel is more oblique and anatomic with trans antero-medial and out-in technique.

The first step in single-stage ACL revision is identifying the previous femoral tunnel removing the remnant graft, debriding soft tissue with an arthroscopic shaver and radio frequency to evaluate tunnel osteolysis and direction, noting that this may increase tunnel size.

If located in a vertical position, leaving the hardware in place could prevent encroachment of the new femoral tunnel into the previous one. The new tunnels are performed in a more horizontal and anatomical position working around the previous hardware.

Sometimes tunnel osteolysis and hardware removal may create bone loss that interferes with desired new anatomical tunnel. Many options have been described for manage these bony deficiencies.

When the old tunnel is in a correct position and larger from 3 to 5 mm than the new graft, then using two interference screws may ensure the graft fills the tunnel [9].

Alternatively, bony defects could be filled with allograft bone, autograft bone (from tibia or iliac crest) and synthetic dowel graft.

Then, using the variable angle ACL drilling guide and sequentially sized reamers, a new tunnel is created: a further option is using an appropriately sized tunnel dilator, centered into the cavitary defect.

When the old tibial tunnel is too posterior (as frequently seen following a transtibial technique) with negligible tunnel widening, a new one, more anterior and anatomic, is performed. Otherwise if the expansion is too big or in case where it is not possible to drill a new tunnel, then a two-stage procedure is indicated.

Two-stage revision

First stage

Standard arthroscopy is performed for the assessment of tunnels and knee joint. Hardware may be left in place if it does not interfere with future tunnel placement. However, hardware removal must always be preferred, when possible. Associated procedures are performed preferably during this stage, such as meniscal and chondral treatment or osteotomy, to correct axial malalignment or tibial slope.

The previous ACL graft, the soft-tissue remnants and sclerotic bone are identified and removed until clean and bleeding bone is exposed to the femoral and tibial tunnel a process involving the shaver, rasps and curettes. The tunnels are then filled in with allograft or autograft bone (from tibia or iliac crest) or synthetic graft. Pre-prepared allograft bone dowels of specific sizes can be used to fill tunnels. The bone graft is impacted into the tunnels, with the allograft being usually 1 mm larger than the diameter of the new tunnel. Lastly, arthroscopic evaluation is performed to check that no bone graft is left into the knee joint.

Second stage

After an interval ranging from 3 to 6 months ACL reconstruction is performed with autograft or allograft. The ACL reconstruction in this setting, is easier such that a primary reconstruction technique can be adopted, with a good bone stock that promotes ligament incorporation and prevents re-injury.

Complications

The literature on complications after ACL revision surgery with allografts is relatively sparse.

With regards to the risk of immuno-mediated response to the graft, modern processing technique have made this complication merely hypothetical, and there are no report of such adverse event in the recent literature [68].

Looking at infection risk, analysis performed on big cohorts of patients or registries documented that the choice of allograft does not imply a higher risk of infection compared to autografts: a Canadian cohort study on 827 revision ACLRs (225 allografts) found a post-operative infection rate of 0.8% (7 patients) requiring surgery and an additional 1.2% (11) treated by antibiotics only. The authors also demonstrated that graft selection (autograft versus allografts of any type) did not influence the risk for infection [41].

In another study, from the Kaiser Permanente ACLR Registry on 1091 (860 allografts) revision ACLRs, the authors reported a similar incidence of 0.8% post-operative infections [44]. The incidence was higher than in primary ACLRs, where an infection rate of 0.3% was documented. In a more recent study from the same Kaiser Permanente ACLR Registry including 2019 patients (1549 allografts), a slightly lower infection rates of 0.6% was documented [4]. An even lower infection rate of 0.15% has been documented in another recent cohort study [71], where the authors found no difference in terms of infection risks between processed and non-processed allograft. In primary ACLR, post-operative infection is relatively uncommon, and in general lower than revision cases [8, 30, 44]. Maletis et al. demonstrated, in their cohort study on 10,626 primary ACLRs (4404 allografts), again from the Kaiser Permanente Registry, that there was no significant increased infection rate in patients reconstructed with allografts compared to BPTB autografts. However, they demonstrated an increased risk of infection when using hamstring tendon autografts compared to both allografts and BPTB autografts [45]. Similar findings have been documented in other studies [8, 32, 34] and in a recent meta-analysis [7]. Two other trials on primary ACLR demonstrated no statistical difference in post-operative infection rates when comparing allografts with BPTB autografts [31] and allografts with both BPTB and hamstring autografts [26].

In a current concept review dating back to 2006, the authors claimed that loss of motion was the most common complication after revision ACL [22]. However, in the recent literature, there are few reports on stiffness after revision ACL. Other complications after knee surgery include deep venous thrombosis (DVT) and pulmonary embolism (PE).

From the Kaiser Permanente ACLR Registry in 2013, DVT was found in 0.2% of 1091 (860 allografts) revision ACL, whereas no PEs were reported [44]. In their recent article, they found DVT in 0.3%, and PE in 0.1% of 2019 (1549 allografts) revision ACL procedures [4]. In neither of these articles did the authors clarify if the complications came in patients reconstructed with allografts or autografts but it seems reasonable to believe that no sub-group difference existed.

In many other studies, the rate of complications after revision ACL is comparable to that of primary ACL reconstruction [21, 22, 27]. Lastly, in a systematic review by Foster et al. authors did not find any significant difference in complication rate in autografts compared to allografts [20]. Based on these findings, ACL revision with allograft seems a safe strategy which does not expose patients to higher risk of post-op early and delayed complications.

Return to sport

Andriolo et al. found in their recent review of the literature, a rate of 82% return to sport in primary reconstructions, versus 75% in revision ACL. The rate of return to an equivalent sport level compared to the pre-injury level was also inferior in revision cases (63% versus 43%) [3]. According to the meta-analysis by Grassi et al. 84% of patients go back to sport but just 52% return to their pre-injury level [25]. These studies did not report data in relation to the specific type of graft used. Factors associated with a higher chance of return to usual sport following revision ACL are: younger age, male sex, professional sports practice, and higher pre-operative functional scores [49].

Few studies have specifically focused on the results of ACL revision performed using allografts, with the majority involving short-term evaluation and only a few studies are comparative trials. Most studies have a retrospective design, including both revisions by autograft and allograft, without clear data on the outcome of "allograft" group. In addition, the evaluation criteria for return to sport are variable, making study comparison extremely difficult. A summary of the most relevant trials concerning return to sport after ACL revision is reported in Table 2.

Only Legnani et al. showed a time span for recovery: it was 7.7 versus 9.8 months, in favor of the autograft group. The rate of return to sport was equivalent for auto and allografts (78 versus 76%) and the rate of return to sport at the previous level was also equivalent (70 versus 67%) [40]. In the study by Ra et al., 100% of the patients were able to go back to sport activity [55]. Patients in this series had a higher pre-injury Tegner score (8.2) compared to that of other reported studies, thus supporting the finding that professional players or patients with higher pre-op functional scores have the best chance of getting back to sport practice.

Table 2 Summary of the most relevant clinical trials reporting data on the outcomes of allograft ACL revision surgery

Authors	Study design	Type of graft	Number of pts	Follow-up
Legnani et al. [40]	Retrospective comparative	HTG versus patellar or achilles tendon	44 (23 auto; 21 allo)	5.2 years
Uribe et al. [64]	Retrospective	Autograft : BPTB or hamstring allograft: BPTB	54 (35 auto;19 allo)	32 months
Battaglia et al. [9]	Retrospective	Autograft : BPTB Allograft : BPTB	63 (43 auto, 20 allo)	72.7 months
Grossman et al. [27]	Retrospective	Auto : contro BPTB Allo (22 BPTB 1 Achilles)	29 (23 allo, 6 auto)	67 months
Johnson et al. [32]	Retrospective	13 allograft BPTB 12 allograft (Achilles)	25 allo	28 months
Gibbons et al. [23]	Prospective	Auto and allo : BPTB	85 (20 auto, 65 allo)	27 versus 42 months
Ra et al. [55]	Prospective	Allograft: Achilles tendon	17	32 months

In a meta-analysis of return to sport after revision ACL reconstruction, six studies (162 patients in total) were included [35]. The average age was 27.1 years (range 16–42), the average follow-up was 41.1 months, and 68% were male. The combined rate of return to sport, independently from the level, was 84% (76–91%), whereas in 64% (56–74%) of cases the same pre-injury level was achieved independently from the type of graft [35].

Based on the data available, the rate of return to sport after ACL revision seems good, although lower when compared to primary ACL reconstruction and there is also overall a lower possibility to get back to the same pre-injury sport activity level [64]. There is no evidence in difference to return to sport according to the allograft selected. However, current literature lacks high-quality randomized controlled trials able to clearly establish if the use of allograft in ACL revision is correlated to a reduced return to sport compared to autografts.

Reported results

When analyzing data comparing results after allograft revision ACL, it is very important to highlight, among other factors, the modality of graft sterilization and preservation, since it has an enormous impact on graft biomechanical properties, and therefore, on the final outcome [60]. Recent studies suggest comparable results using either allografts or autografts up to middle-term evaluation [2, 15].

One of the earliest studies by Gibbons et al. [23] evaluated 66 consecutive patients after ACL revision with allograft irradiated with 25.000 Gy. Complex surgeries (including multi-ligament reconstructions or meniscus allograft) were also included in the study. Patients were evaluated based on clinical examination, KT-1000 and subjective evaluation scores, and the failure rate was 33%. Smith et al. [60] retrospectively evaluated 32 patients after ACL revision surgery (all with non-irradiated BPTB allograft) with a mean follow-up of 4.8 years (from 2.1 to 12.1 years). Results were evaluated based on clinical examination, KT-1000 arthrometry, X-rays, and several questionnaires (IKDC, KOOS, Tegner, Lysholm, Noyes Sport Function, modified Cincinnati, SF-12 Mental, Sf-12 Physical and VAS). Although 9 of 32 patients (28%) had failed, according to authors 88% were almost or completely satisfied. In the systematic review performed in 2015, Andriolo et al. [3], including 59 studies and 5365 patients, 21.4% of revision surgeries were performed using allografts. Overall good objective results and satisfaction rate were reported in 73% of patients (just slightly inferior to primary ACL reconstruction), but only 43% of them returned to the previous level of sport activity. In the meta-analysis by Grassi et al. [24], including 32 papers comparing results after revision ACL with autograft and allograft, it emerged that non-irradiated allografts presented the same outcome as autografts.

In the most recent meta-analysis on revision ACL surgery, Mohan et al. [50] tried to determine objective overall graft failure, failure rate by graft type (allograft versus autograft), instrumented laxity and patients' outcome scores. Among 273 available studies, 8 were selected: all were non-randomized level II studies, fulfilling the inclusion criteria, i.e., measurement of failure rate at minimum 2 years of follow-up. Objective failure rate was defined as graft rupture, need for revision surgery, side-to-side difference > 5 mm (measured with KT-1000/2000), Pivot-Shift + 2/+3. The meta-analysis included a total of 3102 patients, with mean follow-up of 4.8 years and a mean age of 30 years, and 56% patients were male. The overall objective failure rate was 6%, which seems much lower than in previously reported studies (including results after primary ACL reconstruction). Additionally, authors postulated that the difference in failure rate comparing with earlier studies might be also connected with exclusion of retrospective studies in this analysis and improvement of surgical techniques and better recognition and treatment of concomitant pathologies. Furthermore, data were analyzed by graft type: 2302 patients who underwent

autograft reconstruction had a failure rate of 4.1%, whereas 671 patients who underwent allograft reconstruction had a failure rate of 3.6%, meaning that there were no significant differences in terms of failure rate after revision ACL between the autograft and allograft group.

Analyzing data evaluating the results after revision ACL by allograft may be misleading. In many cases, publications have low level of evidence, with retrospective design and lack of objective measurement [13]. Nevertheless, it seems that enough evidence exists to support the following statements: (1) allografts should be rather reserved for revision surgeries, especially in young, active patients; (2) terminal sterilization of allografts with high-dose irradiation should be avoided; (3) the failure rate after revision ACL surgery is comparable between auto- and allografts.

Discussion

The aim of this clinical review was to present the current knowledge on the use of allografts in revision ACL surgery incorporating aspects of biology, graft storage surgical techniques, complications and outcome. Based on the findings of the present review, the use of allografts for ACL revision can be regarded as a safe and effective approach: data from several studies have shown that the infection and overall complication rate, is similar with respect to primary procedures with autografts [45], and also clinical outcomes are satisfactory in terms of durable knee stability after revision and return to sport participation [3, 25].

The use of allografts for performing single or two-stage ACL revision, is well established in many countries but in many the choice of graft type is limited by availability.

We have assessed whether allografts are linked to a greater risk of infection or disease transmission compared to autografts: modern biologic tests performed at the moment of processing the graft and proper sterilization techniques, have shown these risks to be no higher and are just theoretical. Recent data coming from registries have shown that the infection rate following ACL revision with allograft is not increased when compared with ACL revision with autograft [8, 34], and should be related to the intrinsic risks of any surgical procedure. Furthermore, the storage modality of allograft freezing has shown to be reproducible and reliable in preventing microbial growth, thus allowing a safe product to be delivered to the operating theaters [57].

High-dose irradiation has been shown to impair mechanical strength of the grafts. Researchers have identified a threshold to guarantee adequate sterilization of the graft, avoiding the loss of its structural properties: an irradiation dose below 2 Mrad is considered safe for the purpose of maintaining allograft mechanical strength [23, 28]. It should, however, be remembered that even using grafts irradiated at higher doses, it is still possible to achieve good clinical outcome since, once implanted, the graft acts as a scaffold and is re-populated by host cells that ultimately contribute to the neo-ligamentization process that leads to the final integration of the allograft [17, 39].

The use of allograft in the ACL revision surgery depends on many factors such as age, sex, the graft used in the prior treatment, concurrent peripheral lesions and whether the revision is a second or multiple revision procedure. The most used allografts are bone–patellar tendon, semitendinosus, achilles tendon, or tibialis anterior tendons. Bone–patellar tendon–bone (BPTB) allografts have a greater integration capacity, but are less available in tissue banks compared with other grafts [53]. In a recent study, the Multicenter ACL Revision Study (MARS) group demonstrated that the surgeon is the most important factor in ACL revision reconstruction graft choice [47]. This study reported that the most significant factors driving the choice for an allograft were: prior use of autograft, older age, concurrent MCL, posteromedial corner repair, the non traumatic failure, the female gender [46, 47]. It is also essential to evaluate for significant anterior rotatory instability, as extra-articular lateral tenodesis is effective in controlling pivot shift control and decreasing failure rate.

Looking at the clinical outcome following ACL revision with allografts, it seems that a satisfactory return to sport practice could be achieved, with stable results even at middle-term evaluation. Some reports suggest that after allograft revision, there is a lower rate of return to the pre-injury sport activity level, but this could also be explained by a physiological reduction in the frequency of sport practice over time (especially in patients who receive revision surgery many years after primary reconstruction) or due to change in the patients' lifestyle [3]. It is worthy of attention that recent studies [48, 50, 69] on revision ACL reconstruction have shown comparable results, in terms of subjective outcomes and return to sport, using either autograft or allograft, thus confirming that current sterilization and storage techniques are able to preserve the biomechanical properties of allograft tissue. Furthermore, we currently lack evidence concerning the "best" allograft to use for revision ACL: and no significant difference has emerged [35], suggesting that the choice of the graft is based on the surgeons' preference and experience. Based on the available evidence, there is no clear indication on the "ideal" patient that should be treated by allograft reconstruction, both amateurs and professional athletes have been treated by allografts, achieving satisfactory outcomes.

From this review, three categories of patients can be considered the "best candidates" for allograft: (1) those needing ACL revision surgery, where further use of autografts could lead to high relevant donor site morbidity [38]; (2) those affected by complex instability, where there could be the

need of reconstructing other functional structures beyond the ACL [52, 67]; (3) those with clinical and radiologic signs of autologous tendon degeneration (i.e., patellar of hamstring tendinopathy) where the use of autografts could be at risks for lower outcome.

In light of these findings, we consider that the possibility of using allograft for ACL revision should be an available option, always present in the surgeon's armamentarium, especially considering that revision cases are often challenging and deserve to be treated with the best "equipment" possible:

Ultimately, the surgeon should select the right approach for any given specific patients: the final decision should be based on the particular features of the patient, on his/her medical history including previous surgeries and comorbidities, and his/her expectation and functional needs. Autografts and allografts are both suitable options but it is important for the surgeon to have the possibility of choice.

Conclusion

The use of allografts for ACL revision surgery appears a safe and valid option, yielding to satisfactory results in terms of resuming sport practice, with low risks of complications. Allografts should be considered especially in patients with previous multiple ACL reconstructions and with complex instability. Surgeons should carefully consider the use of allografts based on the data summarized in the present review.

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Compliance with ethical standards

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