

# Cadaveric soft tissue allografts and their applications



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# Definition

**Allograft:** The transplant of an organ or tissue from one individual to another of the same species with a different genotype.

Allografts account for many human transplants, including those from cadaveric, living related, and living unrelated donors. Called also an allogeneic graft or a homograft.



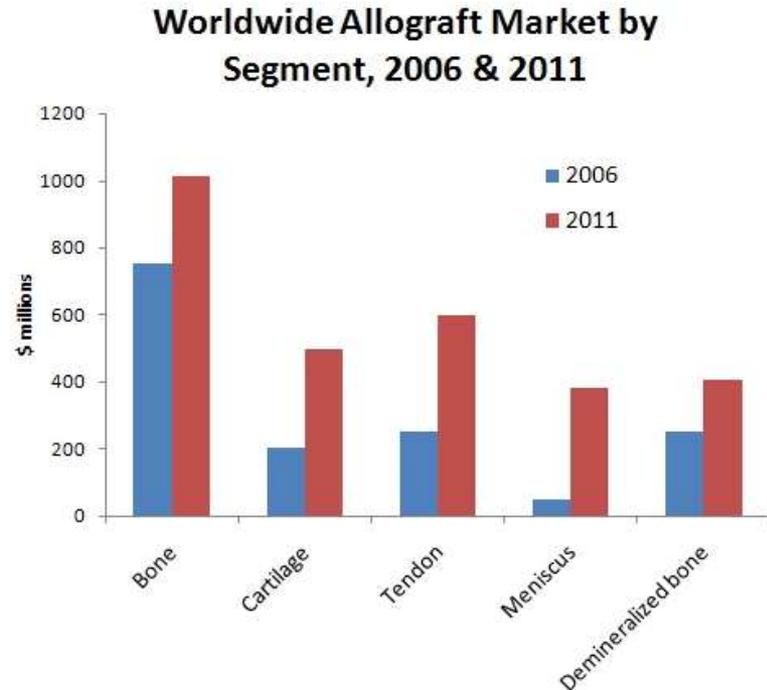
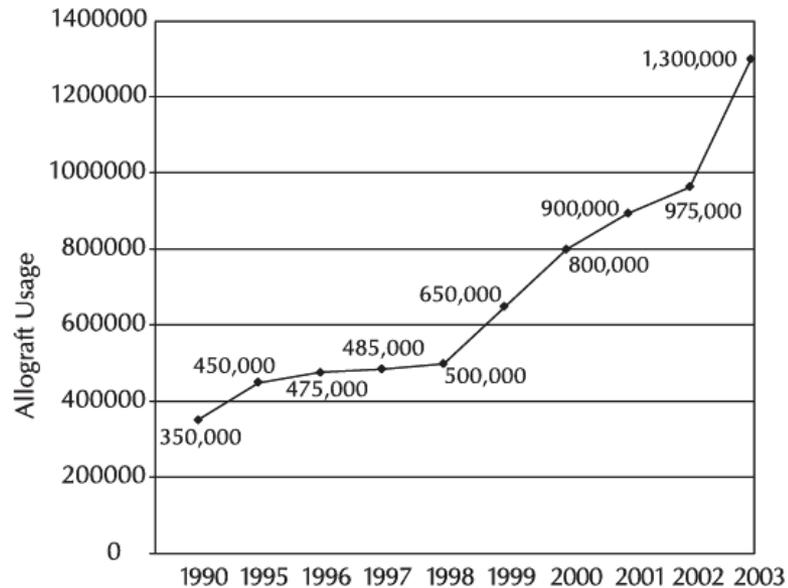
# Historical preview

- 1880** MacEwen first reported the use of allograft bone
- 1925** Lexer reported 23 cases of osteoarticular allograft in the knee (50% success)
- 1981** Noyes and Shino reported good results with allograft ligament reconstruction in the knee
- 1984** First *Standards for Tissue Banking* published by the American Association of Tissue Banks
- 1989** Milachowski reported the first use of human meniscal allografts
- 1994** CDC: Guidelines for Preventing HIV Transmission Through Transplantation of Human Tissue and Organs
- 2002** FDA: Guidance Document - Validation of Procedures for Processing of Human Tissues Intended for Transplantation



*First depicted allograft transplantation. 12th Century painting of Saints Cosmas and Damian. (circa 3rd century)*

# Utilization - marketing



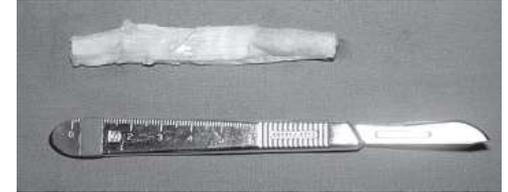
There have been more than 10 million tissue transplants over the past two decades

The global market for all allografts in 2006 is estimated at \$1.5 billion, with bone allografts contributing half of that, soft-tissue allografts \$500 million, and demineralized bone the remaining \$250 million.

# Commonly used Allografts in Orthopaedics

## Bone

- Demineralized bone products (osteoinductive)
- Cortical / cancellous – powder, chips, wedges, dowels, crest, pegs, and screws
- Structural – cortical segments, shafts, long bones, pelvis, acetabulum
- Osteochondral long bone (cryoprotected cartilage)
- Ribs, mandible, calvarium, ear ossicles



## Soft Tissue

- Patellar ligament, Achilles tendon (bone block), hamstrings, tibialis anterior, etc
- Fascia lata, rotator cuff

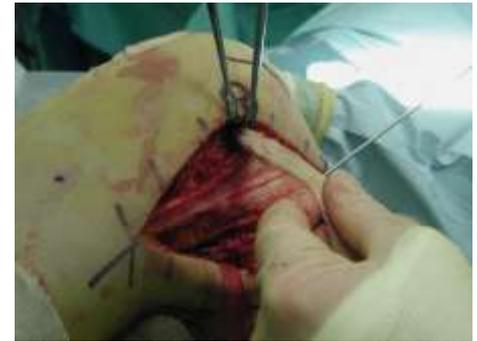
## Cartilage

- Meniscus, osteoarticular segments (fresh and cryoprotected), costal cartilage



# Indications for soft tissue allografts

- reconstruction of ACL
- reconstruction of PCL (tendo Achillis)
- multiple ligament injuries (ACL, PCL, **PLC**)
- patellofemoral instability, chronic patellar tendon rupture
- reconstruction of knee extensor mechanism
  
- reconstruction of ankle lateral ligaments
  
- AC joint dislocation
- elbow instability
- rupture of the pectoralis major tendon
- rupture of the biceps tendon
- chronic triceps insufficiency



# Advantages of allografts

- lack of donor site morbidity
- high tensile strength
- decreased surgical time
- smaller surgical incisions
- low risk of arthrofibrosis
- use in multiple ligament injuries
- use in revision surgery
- immature skeletal growth



**Double-band PCL and single band ACL with Achilles tendon and BPB allograft**

# Disadvantages of allografts

- availability
- high cost
- weakness due to sterilization process
- longer time for remodeling & incorporation
- susceptibility to rejection
- potential risk for bacterial, viral and prion disease transmission



# Accreditation



American Association of Tissue Banks

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At AATB,

*We Help To Change Lives.*

# Accreditation

<http://www.aatb.org/>

An organization critical to the regulation of tissue banks is the AATB. Founded in 1976, the AATB is a nonprofit organization to spread voluntary safety standards

Currently, the AATB has 106 accredited tissue banks, and it has been estimated that AATB-accredited tissue banks distribute 90% of musculoskeletal tissues in the United

The “committee on biological implants tissue work group” of the AAOS have urged the orthopedic surgeons to work with AATB tissue banks and “know their tissue banker”.

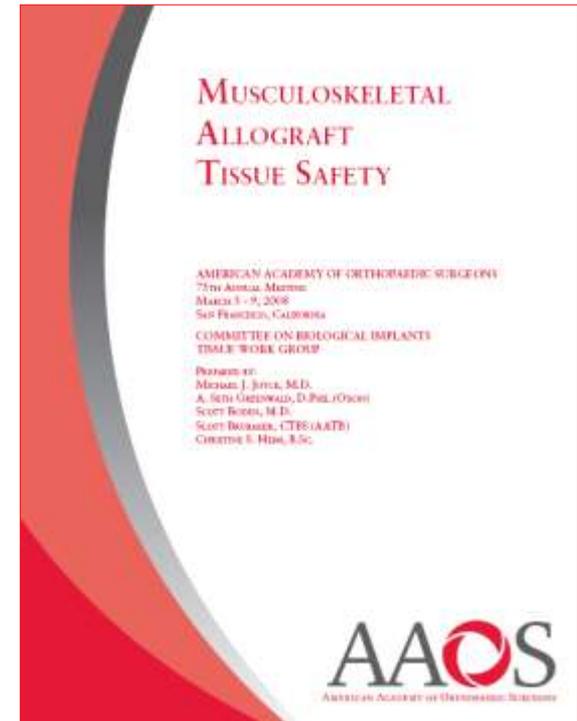
Other authors have stated that a tissue bank not accredited by the AATB should be “a red flag” with respect to quality

# Safety

## Standards for Tissue Banking (1984)

- (1) obtaining a detailed medical, social, and sexual history
- (2) a physical examination with specific attention to hepatosplenomegaly, lymphadenopathy, and the presence of cutaneous lesions
- (3) the result of the autopsy (if performed) to be included in the tissue procurement workup
- (4) the following tests on donor serum: HIV I and II, hepatitis surface antigen, hepatitis C antibodies, syphilis antibodies, and T-cell lymphotropic virus antibodies

All of these precautions, along with sterile procurement, facilitate the safety of allograft tissue



# Procurement

## 1. Medical History and Behavioral Risk Assessment

### Exclusionary Criteria:

- |   |   |
|---|---|
| <ul style="list-style-type: none"><li>• Active infection, sepsis, or TB</li><li>• History of systemic viral illness (Hepatitis, HIV, recent West Nile Virus)</li><li>• Untreated syphilis, Hansen's Disease</li><li>• Certain autoimmune diseases</li><li>• Exposure to toxic substances that may affect tissues</li><li>• Rheumatoid arthritis, systemic lupus, polyarteritis nodosa, or sarcoidosis</li></ul> | <ul style="list-style-type: none"><li>• Clinically significant metabolic bone disease</li><li>• Clinically significant malignancy</li><li>• Implantation of dura mater or use of human derived pituitary growth hormone (Spongiform Disease, CJD)</li><li>• Risk factors associated with HIV (including Group O), viral hepatitis, hepatitis, sepsis, WNV, malaria, and vCJD</li><li>• Dementia of infectious or unknown etiology</li></ul> |
|---|---|

# Procurement

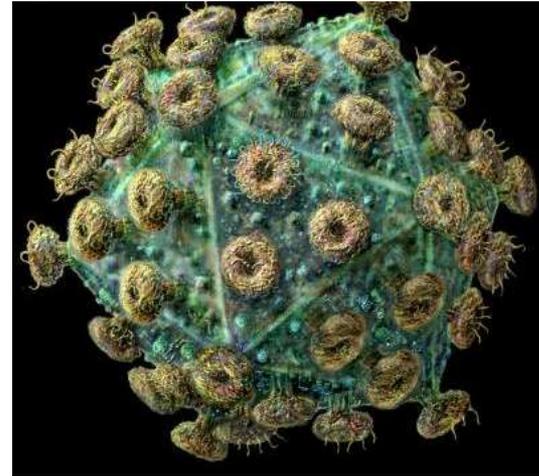
## 2. Physical Assessment (looking for evidence of)

- Active infection: viral, bacterial, or fungal
- Sexually transmitted diseases such as genital ulcerative disease: herpes simplex, syphilis and chancroid
- Needle tracks (drugs) recent tattoos and piercings (past 12 months)
- Lymph node enlargement
- Jaundice, icterus, hepatomegaly
- Blue/purple (gray/black) spots consistent with Kaposi's sarcoma
- Evidence of anal intercourse (perianal lesions, insertion trauma)
- Unexplained oral thrush
- Trauma or infection to recovery sites
- Clinically significant skin lesions (rash, scabs)

# Procurement

## 3. Infectious Disease Testing (tests Required by FDA)

- HIV 1/HIV 2 Antibody/HIV-1 (NAT)
- HB Core Antibody (total, IgM and IgG)
- HBsAg
- HCV Antibody/HCV (NAT)
- Syphilis test (*T. pallidum*)
- HTLV-I/II Antibody



HIV

**Hepatitis B** - One case: *Shutkin, JBJS 36A:160-162, 1954*

**Hepatitis C** - One case: *Eggen and Nordbo, NEJM 326:411, 1992*

Two cases: *Conrad et al, JBJS 77A:214-224, 1995*

Four cases: three bone-tendon-bone (non-irradiated) and one tendon: *MMWR 52(13):273-276, April 4, 2003; Tugwell et al, Ann Intern Med 143(9):648-654, 2005*

**HIV** - One case: *MMWR 37(39):597-599, 1988* (pre-HIV antibody testing)

Three cases: *Simonds et al, NEJM 326:726-732, 1992* (tissue recovered in 1985)

# Procurement

## Infectious Disease Testing (tests Required by FDA)

Since 2005, the AATB requires the use of the Nucleic Acid Test (NAT) for HIV and HCV, which substantially reduces the “window period.” (FDA emerged this test in 2007)

The AATB is also strict regarding culture results. It requires that any processed allograft that tests positive for **Clostridium** or **Streptococcus pyogenes** be discarded.

Window Period Period between infection and time virus is detectable by screening tests.		
Virus		
	HIV	HCV
Window Period using FDA Licensed Tests	HIV antibody 22 days NAT* - 7 days	HCV Antibody 70 days NAT* - 7 days
Blood Donor Estimated Risk (repeat donor) (a)	with NAT* 1:2 million	with NAT* 1:2 million
Tissue Donor Estimated Risk (b)**	without NAT* 1:55,000 with NAT* 1:173,000	without NAT* 1:42,000 with NAT* 1:421,000

\*Nucleic Acid-Amplification Test  
Source: (a) Stramer et al, NEJM 351:760-768, 2004  
(b) Zou et al, NEJM 351:751-759, 2004

**Based on reports in the literature, the incidence of infections is estimated to be 0.02% from around 20,000 transplants a year and 0.0004% from around 900,000 allografts per year**

# Processing

- Aseptic conditions under standard sterile operating room techniques, yet contamination can be introduced by the human handling the tissues.
- Tissue procurement must take place within 24 hours of asystole if the body is cooled or 15 hours if the body is not cooled
- As each tissue is obtained, it is cultured, wrapped, labeled, and sealed in dedicated containers at wet ice temperatures.
- Surface swab cultures are performed to evaluate for the presence of bacteria and fungi; Studies have shown that surface swab cultures are only 78% to 92% sensitive



# Sterilization

Tissue bank	Sterilization method
AlloSource	SterileR validated bioburden reduction cleansing system followed by low-dose terminal irradiation to provide SAL $10^{-6}$ . Package is labeled "sterile."
Bone Bank Allografts	GraftCleanse: proprietary blend of cleansing agents used to reduce bioburden and provide aesthetic white appearance. GraftCleanse: terminal low-dose gamma irradiation achieves package sterility.
Community Tissue Services (CTS)	Musculoskeletal grafts are soaked and rinsed in antibiotics, hydrogen peroxide, alcohol, sterile water, and AlloWash solutions. Low-dose terminal gamma irradiation is used to eliminate most bacteria.
LifeNet	AlloWash XG: rigorous cleansing removes blood elements followed by decontamination and a scrubbing regimen to eliminate bacteria and viruses. Tissue is terminally irradiated at a low dose to reach SAL $10^{-6}$ and is labeled "sterile."
Musculoskeletal Tissue Foundation (MTF)	MTF processes soft tissue allografts aseptically and treats the grafts with an antibiotic cocktail of gentamicin, amphotericin B, and imipenem and cilastatin sodium (Primaxin). Some incoming tissue is pretreated with low-dose gamma irradiation to reduce bioburden. No terminal irradiation used.
OsteoTech	OsteoTech processes allograft tissue using aseptic technique in class 100 clean rooms. Isolators are used to prevent cross-contamination.
RTI Biologics, Inc.	BioCleanse: an automated chemical sterilization process that is validated to remove blood, marrow, and lipids and eliminate bacteria, fungi, spores, and viruses while maintaining biomechanical integrity and biocompatibility. No preprocessing or terminal irradiation is used on sports medicine allografts. All tissues reach SAL $10^{-6}$ post-BioCleanse.
Tissue Banks International (TBI)	Clearant Process: pathogen inactivation process involving high-dose gamma irradiation at (5.0 Mrad) combined with radioprotectant that sterilizes tissue in the final packaging, significantly inactivates infectious agents, and maintains the function of the allograft.

# Storage

- **Cryopreservation:** Grafts are initially cooled to 0°C and processed within 48 hours of donor death. After decontamination with antimicrobial solutions, allografts are subjected to controlled-rate freezing to -135°C and packed in a cryoprotectant solution. Cryopreserved grafts can be stored at -196°C for as long as 10 years.
- **Deep-freezing** is the simplest and most widely used method of ligament and meniscal allograft storage. Freezing to -80°C is typical for frozen storage. It can then be stored for 3 to 5 years.
- **Freeze-drying** (lyophilization) can be used for ligament and meniscal allografts. The graft can then be vacuum packaged and stored at room temperature for up to 3 to 5 years. Rehydration of freeze-dried ligament grafts with attached bone plugs requires a minimum of 30 minutes before implantation.



## Clinical and surgical considerations

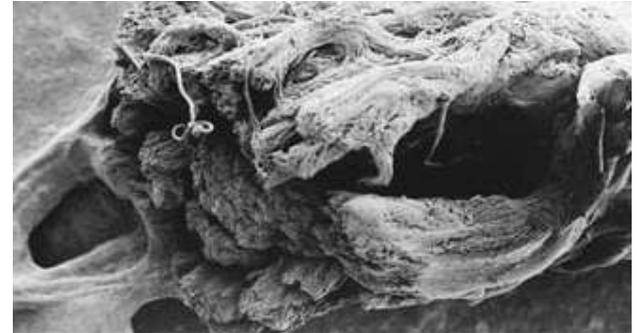


# Incorporation & Biomechanics

- Once implanted, allografts are a scaffold for host tissue ingrowth. Allografts progress through four stages of healing: cell necrosis, revascularization, cellular repopulation, and remodeling.

- **Drez** concluded that freeze dried allograft were biomechanically and biologically similar to patella tendon up to 52 weeks autografts in a goat model

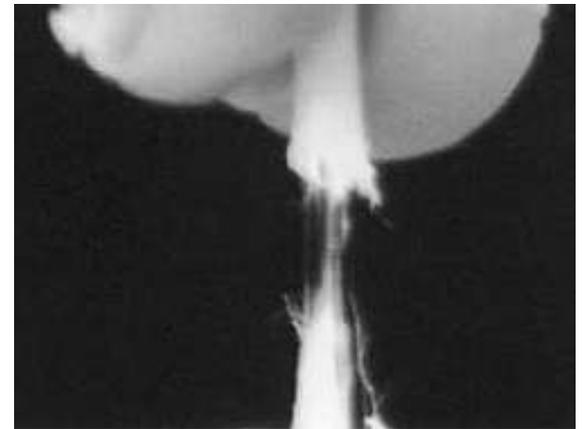
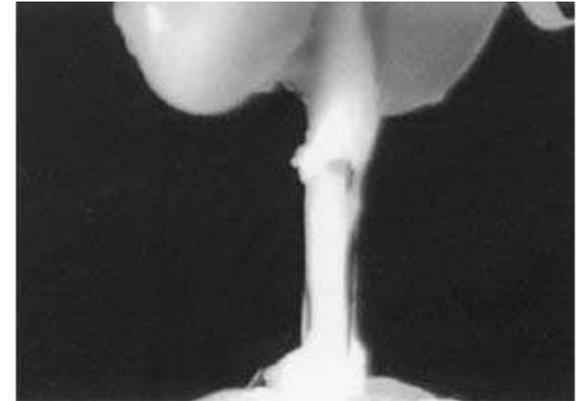
- **Jackson**, however, demonstrated a slower rate of incorporation of allografts at six months



## Incorporation & Biomechanics

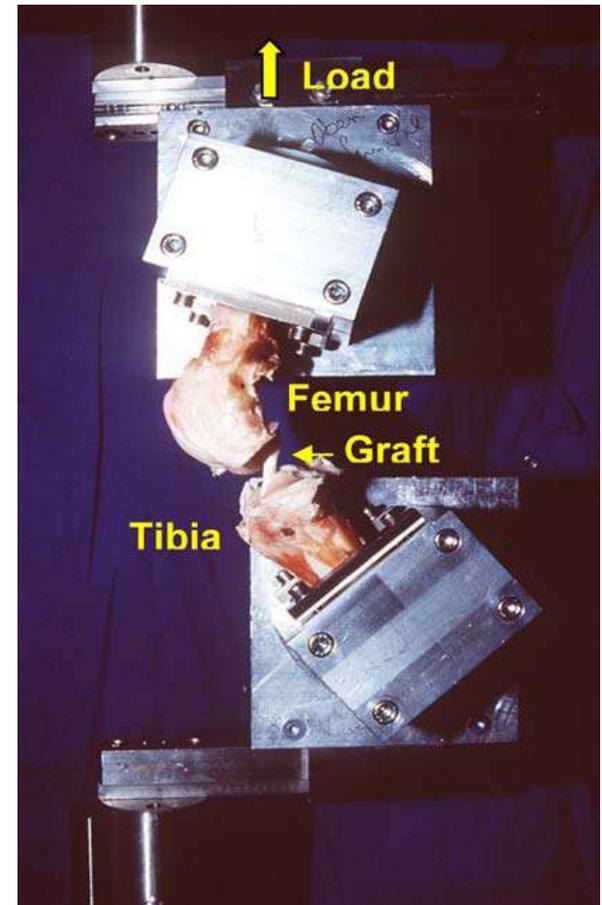
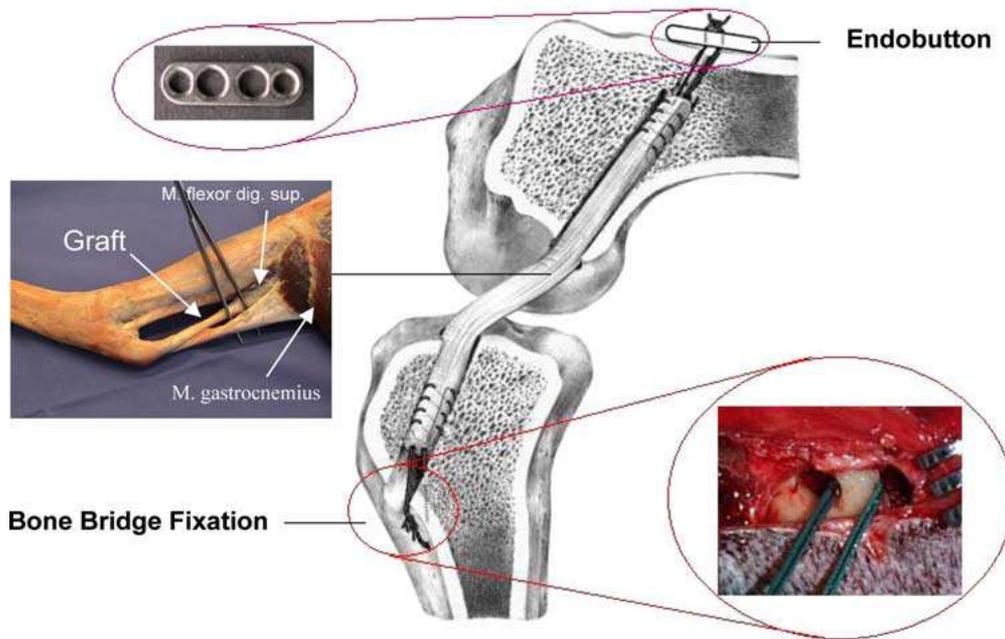
- **Shino** estimated that the mean maximum tensile strength of tendon allografts, in a dog model at 30 weeks after implantation, was only 30% of the strength of the anterior cruciate ligament in the control limb.
- **Curtis** demonstrated that freeze dried fascialata allografts achieved a mean maximum load to failure at 24 weeks of 536 Newtons compared to 801 Newtons in the contralateral knee, with an intact ACL.

It appears that allografts may achieve at best 50% of the strength of the anterior cruciate ligament and that the rate of recovery of strength may be slower than autografts, although both achieve similar levels of strength at final maturation, possibly after 18 months.



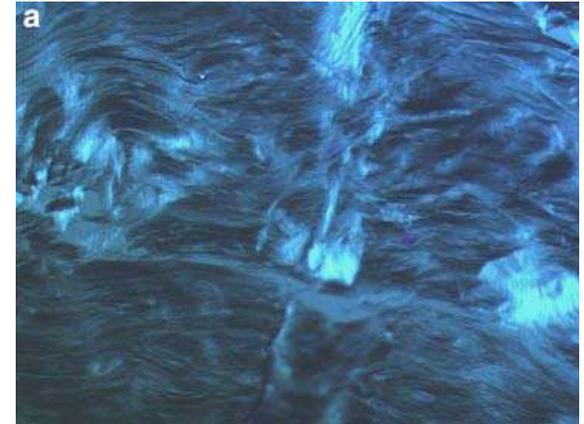
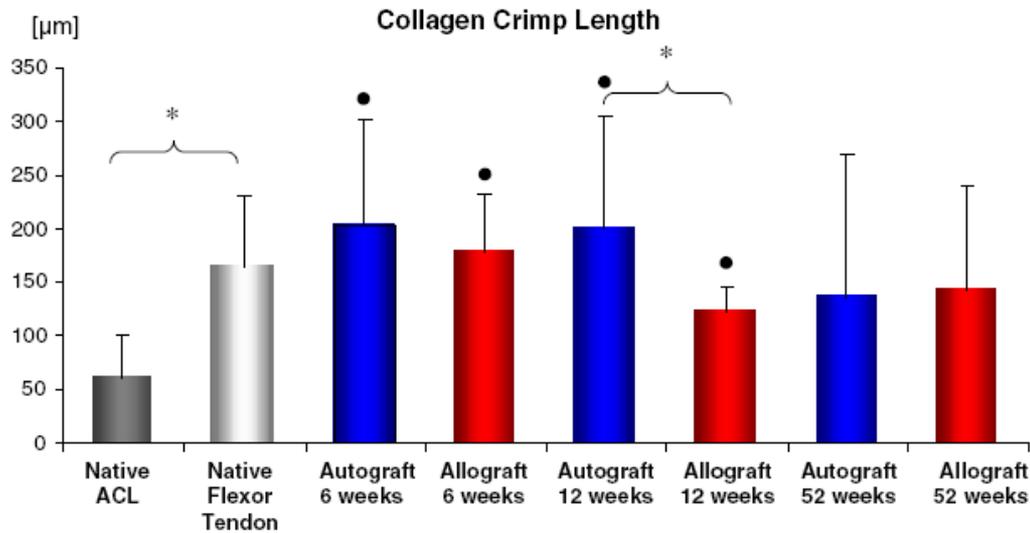
## The extracellular remodeling of free-soft-tissue autografts and allografts for reconstruction of the anterior cruciate ligament: a comparison study in a sheep model

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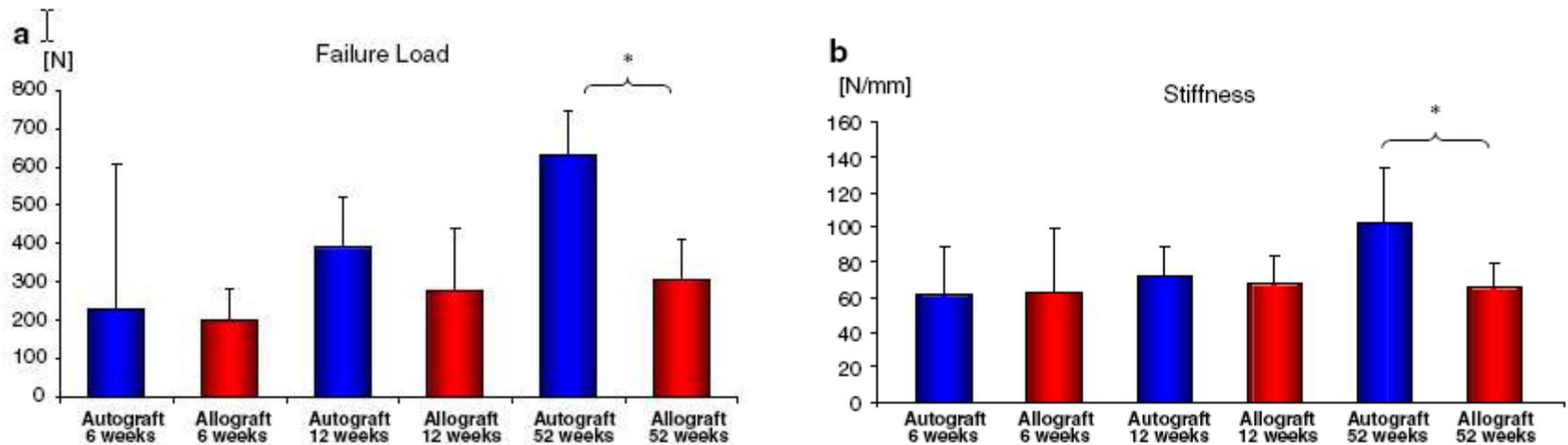
autograft



allograft

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Extracellular remodeling of allografts develops slower than in autografts. Therefore, rehabilitation procedures will have to be adapted according to graft and patient selection.

## A literature review of autograft and allograft anterior cruciate ligament reconstruction

Jonathan Marrale · Matthew C. Morrissey ·  
Fares S. Haddad

**Table 2** Clinical trials, in chronological order, comparing allograft and autograft anterior cruciate ligament reconstruction

Author	N	Follow-up	Main findings
Lephart et al. [64]	33	12,24/12	No significant differences in strength/function.
Saddemi et al. [95]	50	24,52,104/52	No significant differences in perioperative morbidity. Two persistent effusions in the allograft group, two flexion contractures in the autograft group.
Shino et al. [104]	92	18–36/12	Better anterior stability and recovery of quadriceps strength at 60°/s in the allograft group.
Harner et al. [39]	90	45/12	No significant differences except loss of terminal extension in the autograft group (not clinically significant).
Stringham et al. [106]	78	34/12	No significant difference in subjective results or effusions, range of movement, atrophy, or tenderness. Trend toward better stability in the autograft group and better quadriceps strength in the allograft group but this was not statistically significant. Four traumatic ruptures in the allograft group.
Shelton [98]	60	3,6,12,24/12	No significant differences in objective outcome measures.
Victor [109]	73	6,12,24/12	Greater anterior translation in autograft group at 6 and 12/12 but at 24/12 the allograft group showed more anterior translation. Greater quadriceps strength in the allograft group at 6 and 12/12 but greater in the autograft group at 24/12. Re-rupture in three allografts.
Peterson [85]	60	3,6,12,24,63/12	Equivalent patient satisfaction and objective results. Greater loss of extension in the autograft group but not clinically significant.
Chang [21]	79	33–40/12	No difference in subjective scores, anteroposterior stability, crepitus or patello femoral pain. More allografts had flexion deficits and there were three cases of traumatic rupture in the allograft group.
Kustos et al. [62]	79	38/12	No significant difference in Lysholm, Tegner and IKDC scores. Two traumatic ruptures in the allograft group, one in the autograft group.
Poehling et al. [87]	159	Pre-op; 1 and 6/52; 3 and 6/12 and annually for 5 years	Similar long term results in both groups. Less pain and better function in allograft group during first year.

## A literature review of autograft and allograft anterior cruciate ligament reconstruction

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**Allograft**



**Autograft**

Comparison trials of allograft and autograft have largely shown little difference in outcome between the two but they are limited by the fact that they have not been prospectively randomised. Large, well-controlled, prospective studies reporting the long-term (>5 years) results of ACLR are still needed to define the optimal surgical treatment of the ACL deficient knee

## A Meta-analysis of Patellar Tendon Autograft Versus Patellar Tendon Allograft in Anterior Cruciate Ligament Reconstruction

Aaron J. Krych, M.D., Jeffrey D. Jackson, M.D., Tanya L. Hoskin, M.S.,  
and Diane L. Dahm, M.D.

Inclusion criteria of studies included:

- (1) Comparative studies of BPTB autograft with prospective data;
- (2) a minimum 2-year follow-up;
- (3) Identical rehabilitation protocols;
- (4) Subjective and
- (5) objective assessment of outcome.

Allografts other than BPTB (Achilles, tibialis anterior tendon, etc.) were excluded.

Of 548 studies, 6 fulfilled the inclusion criteria, with 256 patients in the autograft and 278 patients in the allograft group.

*Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 24, No 3 (March), 2008: pp 292-298*

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In this meta-analysis, graft failure and functional outcome as measured by single-leg hop test favored ACL reconstruction with BPTB autograft over BPTB allograft.

However, when irradiated and chemically processed grafts were excluded, no significant differences were found in all measurable outcomes.

Jeffrey A. Rihn  
James J. Irrgang  
Anikar Chhabra  
Freddie H. Fu  
Christopher D. Harner

## **Does irradiation affect the clinical outcome of patellar tendon allograft ACL reconstruction?**

There was no difference in IKDC Subjective Knee Scores between groups (86.7 allograft vs. 88.0 autograft,  $p=0.65$ ).

The average maximum manual KT-1000 side-to-side difference was 1.3 and 2.2 mm for allograft and autograft

90.6% of the allograft and 82.8% of the autograft had normal/nearly normal overall IKDC physical examination rating

66.7% of the allograft and 77.8% of the autograft returned to the same or more strenuous level of sports

ACL reconstruction with irradiated allograft BPTB had similar clinical outcomes compared to those reconstructed with autograft BPTB.

## **Anterior cruciate ligament reconstruction with BPTB autograft, irradiated versus non-irradiated allograft: a prospective randomized clinical study**

Kang Sun · Shaoqi Tian · Jihua Zhang ·  
Changsu Xia · Cailong Zhang · Tengbo Yu

Most importantly, 87.8% of patients in the Autogroup, 85.3% in the Non-Ir-Auto group and just only 31.3% in the Ir-Allo group had a side-to-side difference of less than 3 mm according to KT-2000.

The failure rate of the ACL reconstruction with irradiated allograft (34.4%) was higher than that with autograft (6.1%) and non-irradiated allograft (8.8%). The anterior and rotational stability decreased significantly in the irradiated allograft group.

## **A meta-analysis of stability of autografts compared to allografts after anterior cruciate ligament reconstruction**

Chadwick Prodromos · Brian Joyce ·  
Kelvin Shi

**Chang** found a 7% rate of late allograft traumatic rupture versus none in his autografts.

**Olson** found an increasing allograft laxity over time.

**Paulos** found identical two-year auto and allograft stability rates but at 5 years the allograft failure rate was substantially higher than that of the autografts

**Malinin** found significant portions of allografts as late as 3 years post-operatively with neither vascular nor cellular ingrowth.

**Siegel** found significant deterioration in initially good allograft stability rates 10 years after implantation and also found acellularity in long term biopsy specimens

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**Table 3** Possible causes of increased allograft clinical laxity and sources of additional information

Immunologic response	Schulte, Jackson
Freezing	Cryolife
Lack of cryopreservation	Cryolife
Increased donor age	Kurzweil
Increased graft shelf time	sterling
Subclinical infection	Carpenter
Radiation Sterilization	Noyes, Gorschewsky

In conclusion, despite some reports of high stability, the literature has shown ACLR allografts to have overall substantially lower stability rates (3 times less) when compared to autografts.

# Conclusions

Safely procuring and processing the grafts and thorough screening of donors have improved the quality of the allograft pool and decreased the risk of disease transmission. **This risk is reduced but not eliminated!**

As recommended by AAOS surgeons need to be **familiar with the tissue bank** they work with and how their grafts are processed

An understanding of the comparative remodelling between auto- and allograft and the likely effects of processing may be used to help the choice of graft used and to **direct rehabilitation** to minimise the risk of rupture.

A comprehensive **discussion with the patient** and family members is imperative. The risks, benefits, and alternatives must be clearly explained during the consent process.

Thanks for your attention



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