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Update on Ligament Fixation

Biological Enhancement


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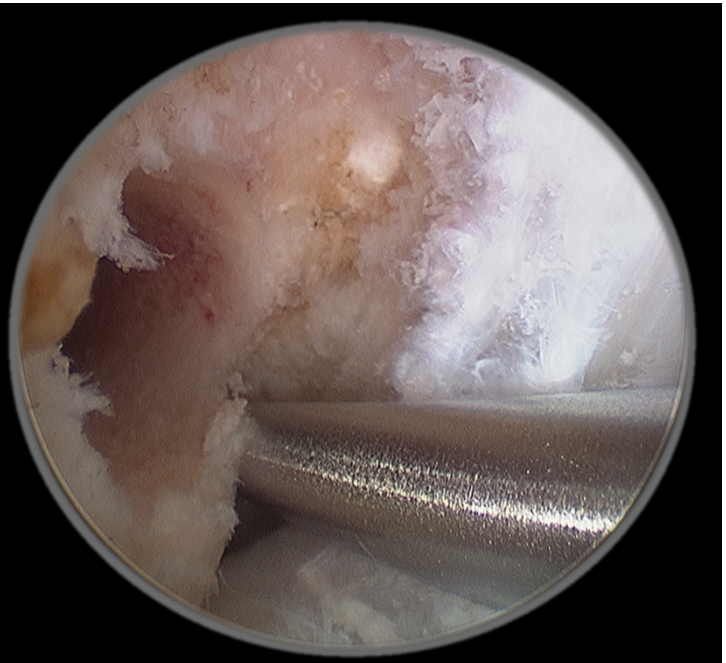
Disclosures

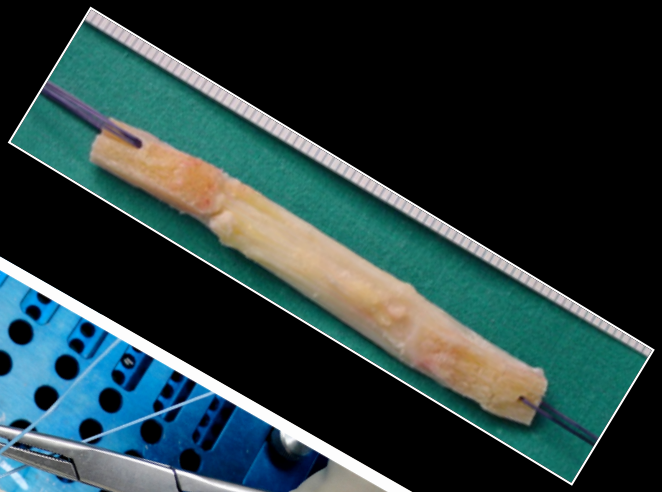
- Consulting with ConMed-Linvatec
- Consulting with Surgival
- Cosulting with Bioiberica
- Editorial Committee of *Arthroscopy*
- Educational Committee of ISAKOS
- Arthroscopy Committee of ESSKA
- I do not have any conflict of interest related to this presentation

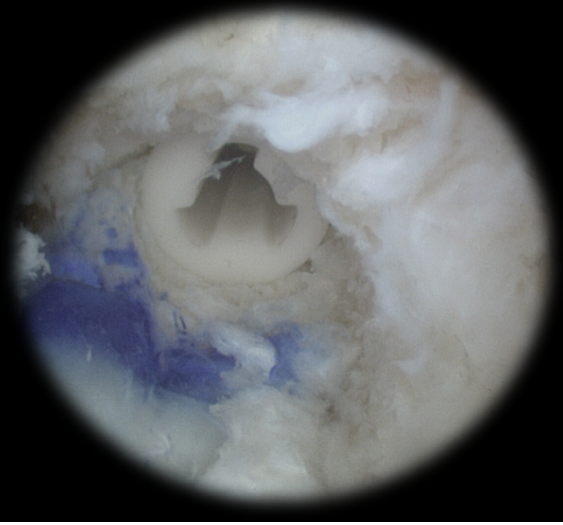
Overview



Good ACL Reconstruction requieres:

- bone tunnel construction and placement
- graft choices and preparation
- graft fixation



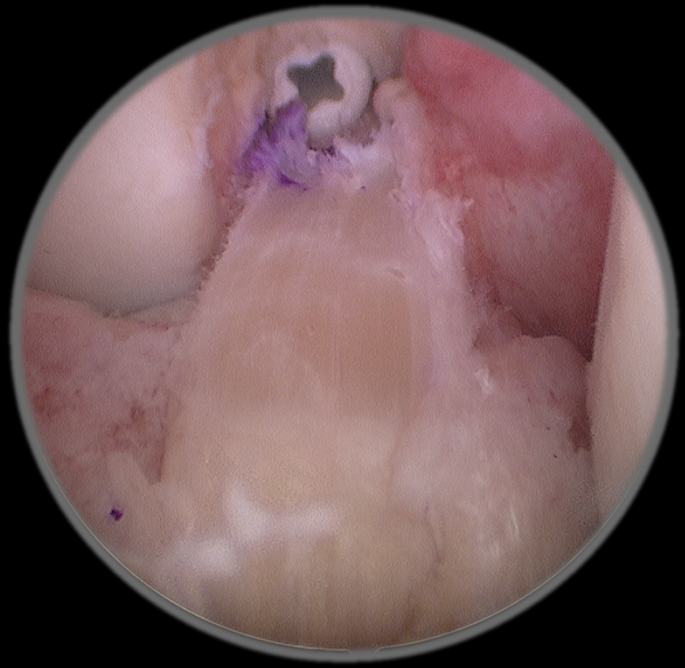


But…

Perfect surgical techniques still need an adequate biological healing response to yield good clinical outcomes

*poor graft healing is one of the causes leading to nontraumatic ACLR failure

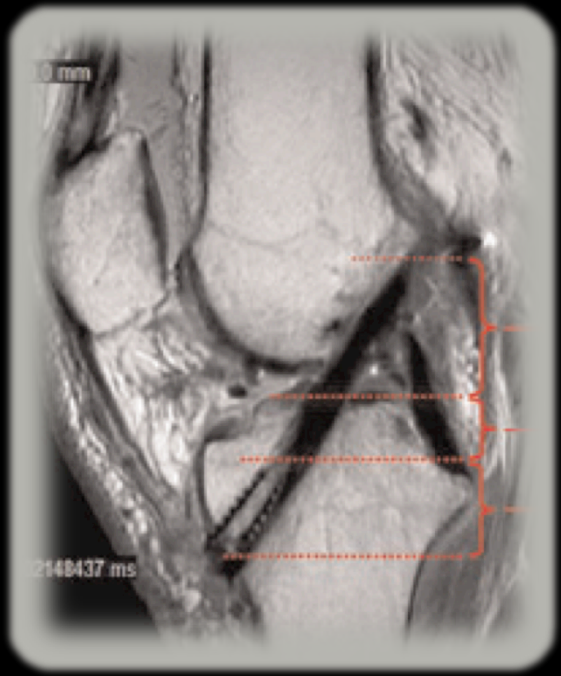
Carson 2004, Ekdahl 2008



Graft healing of ACLR involves slow biological processes:

- **Graft remodeling**
  - Intratunnel graft incorporation
  - **Intraarticular graft ligamentization**

Gulotta 2007

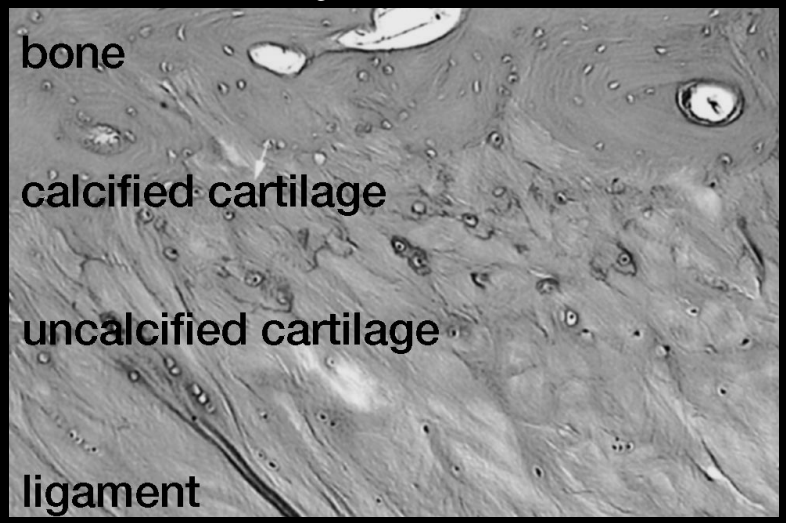


ACL INSERTION SITE

Normal insertion site anatomy of the ACL has a specific arrangement of :

- Collagen fibers
- Fibroblasts
- Fibrochondroblasts
- Osteoblasts

Direct ligament insertion



distribute longitudinal and shear forces from the ligament into the subchondral bone plate

minimizes stresses on individual collagen bundles

Benjamin M, Evans EJ, Copp L. The histology of tendon attachments to bone in man. *J Anat.* 1986

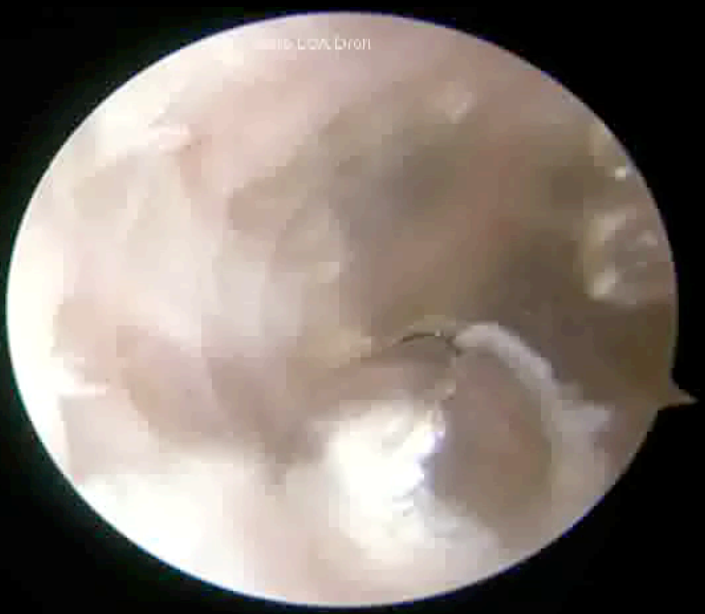
INSERTION SITE HEALING

This complex anatomy →

not restored by conventional free tendon transfers

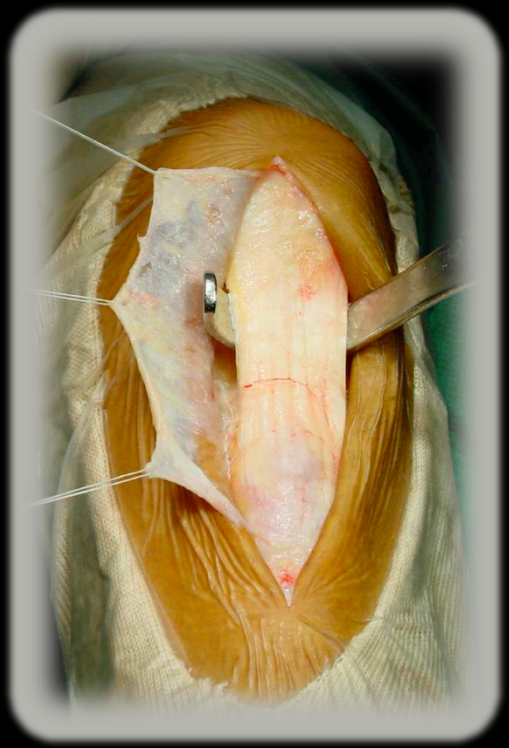
* soft tissue fixation predominantly composed of fibrous tissue aligned

along the load axis

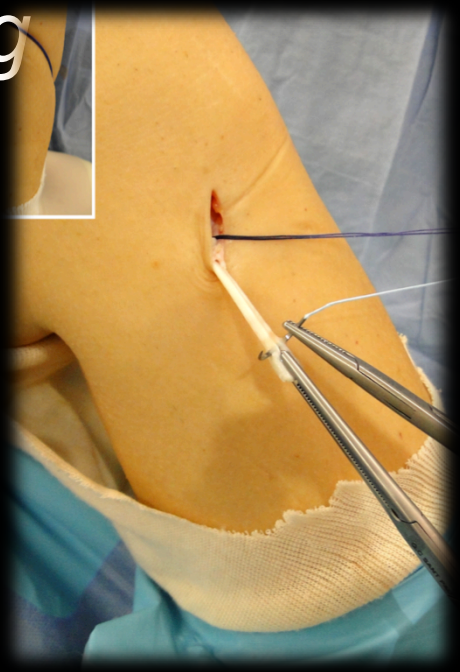


Shino K. Replacement of the anterior cruciate ligament by an allogeneic tendon graft: An experimental study in the dog. *JBJS Br* 1984

BONE TUNNEL HEALING



The mechanism by which graft-bone healing occurs depends on the type of the graft used.



Biology of ACL Reconstruction

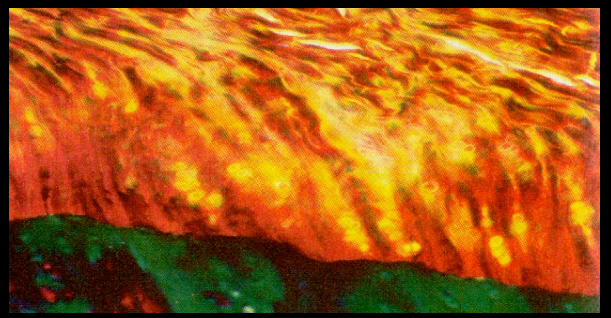
Bone to Bone Healing

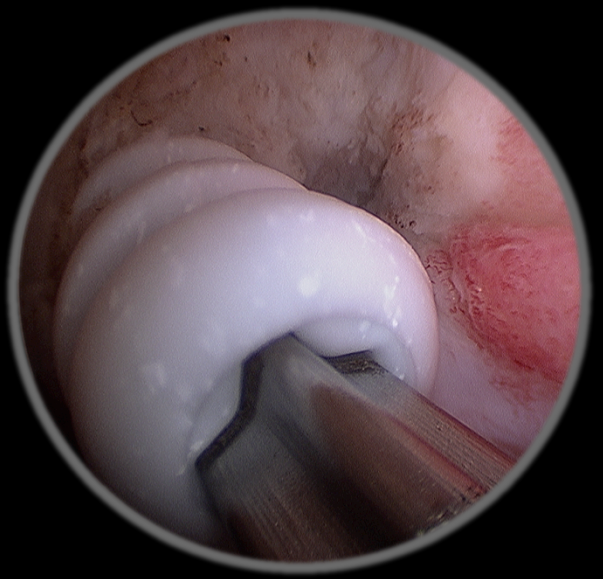
- Resembles normal fracture healing

  ➔ 6-8 weeks

  * Complete incorporation of the bone block in the tunnel observed ➔ 16 weeks

- B-PT-B grafts have the advantage of allowing rigid fixation of the graft in the bone tunnel



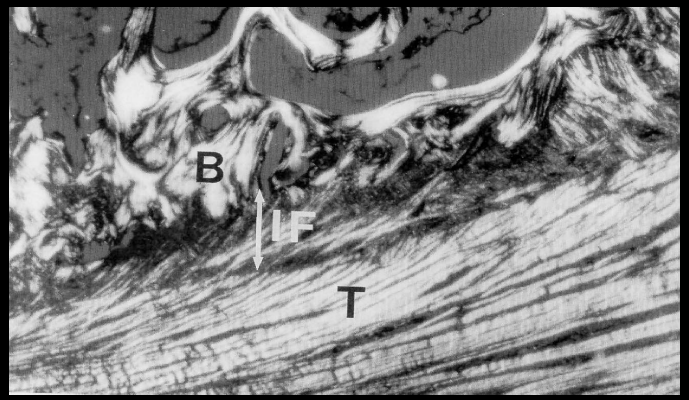


Grana *AJSM* 1994, Fu *AJSM* 1999

Biology of ACL Reconstruction

Tendon to Bone Healing

- Fibrovascular interface tissue between graft and bone
- Progressive mineralization of the interface tissue
- Bone ingrowth into the outer tendon
- Incorporation of the tendon graft into the surrounding bone (Sharpey-like fibers formation)
  *indirect marker of tendon to bone healing



Takes a long time ➔ 12 weeks

Rodeo 1993, Eriksson 2008, Chen 2009

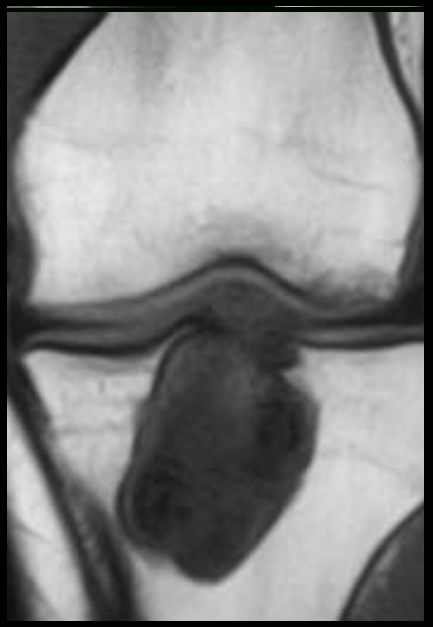
Complete tendon to bone tunnel healing

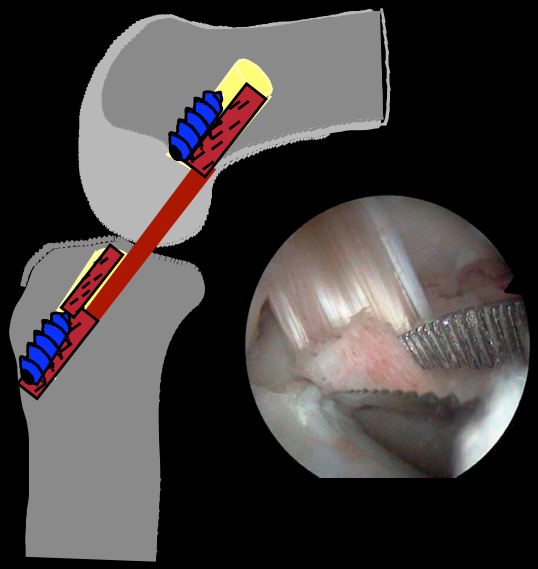
➔6 to 12 months

Nebelung 2003, Hays 2008

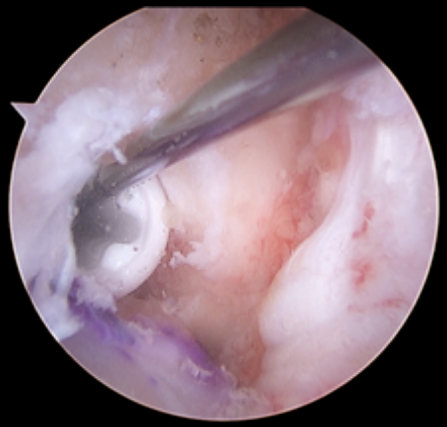
GRAFT TUNNEL HEALING

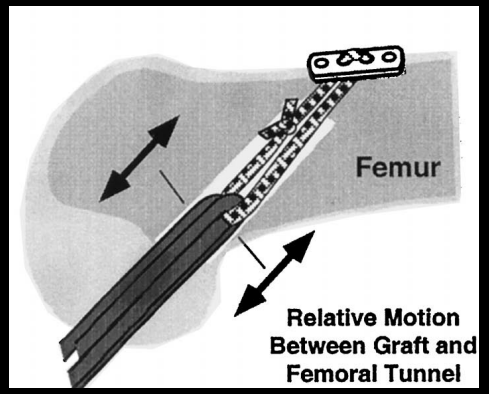
- Graft tunnel motion
- Tunnel widening





Injerto túnel tibial





Fu *AJSM* 1999

STRATEGIES TO ENHANCE TENDON TO BONE HEALING

Strategies to enhance Tendon graft to bone healing

- Brushite calcium phosphate cement
- Injectable tricalcium phosphate
- Calcium phosphate
- Magnesium-based bone adhesive
- Demineralized bone matrix

Biomaterials

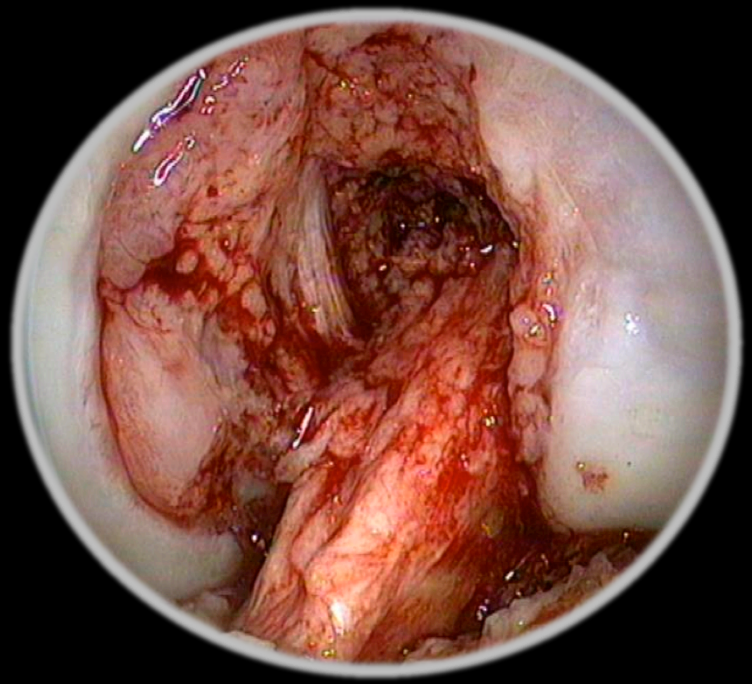
- Bone marrow
- Bone morphogenetic protein-2 (BMP-2)
- Transforming Growth Factor-β1 (TGF-β1)
- Mesenchymal stem cells
- Granulocyte colony-stimulating factor

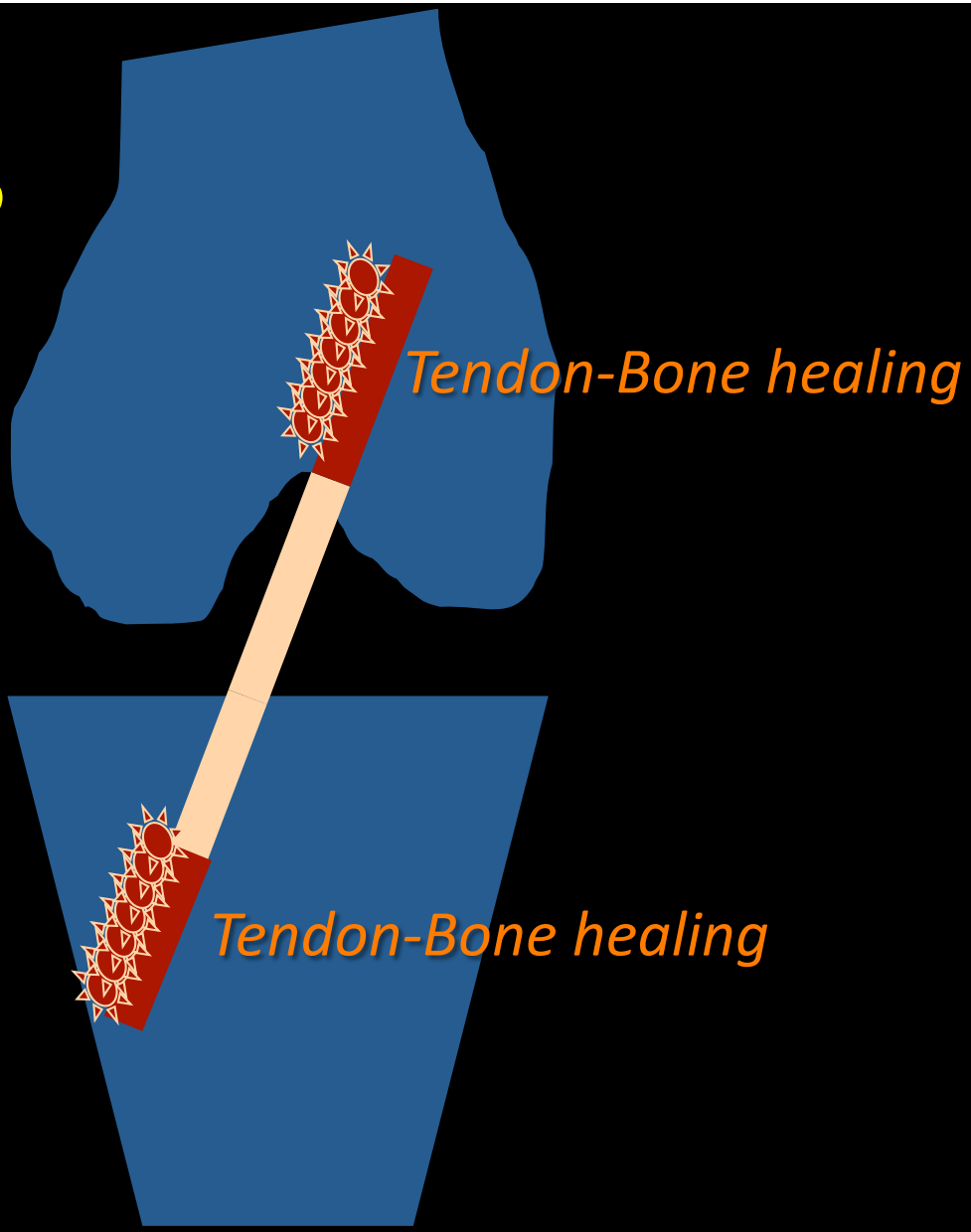
GF & MSCs

- Hyperbaric oxygen treatment
- Low-intensity pulsed ultrasound
- Shock wave therapy

Physical Agents

Clinical studies





Experimental studies

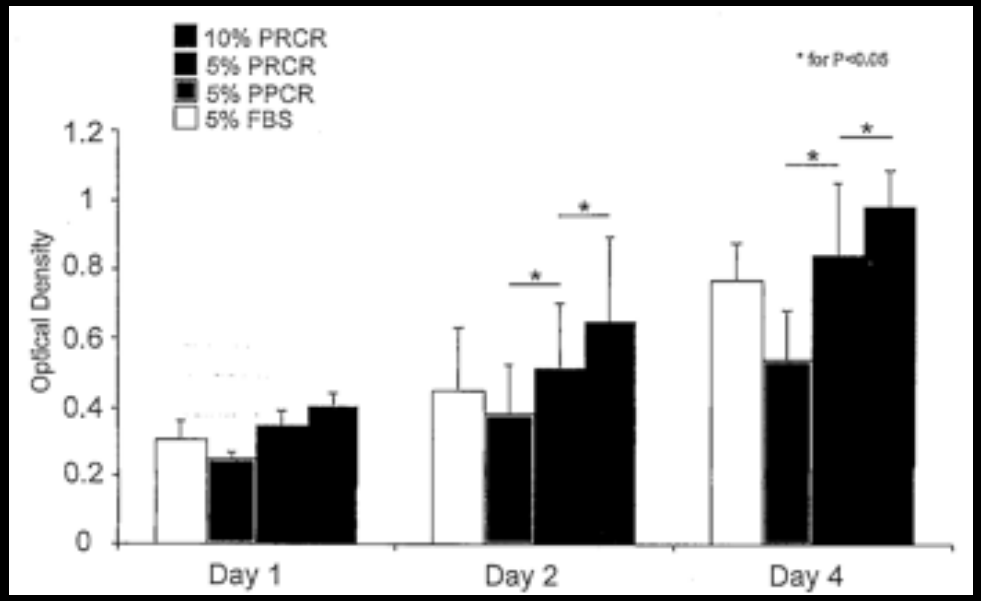
GF & MSCs

ACL Reconstruction

PRP

In vitro ➔

- Platelet rich plasma improves ACL cells viability and function



Fallouh et al. Effects of autologous platelet-rich plasma on cell viability and collagen synthesis in injured human anterior cruciate ligament. *J Bone Joint Surg Am* 2010

GF & MSCs

PRP
Rationale of use

- ***Early administration*** *of PRP (during the inflammatory process) may lead to an* ***accelerated healing cascade*** *(shorter than the typical period expected for full graft maturation and integration)*

The goals

to increase histologic metrics in repair and remodelling of the graft

to improve tunnel healing

to decrease donor site morbidity

Sánchez et al. Ligamentization of tendon grafts treated with an endogenous preparation rich in growth factors: Gross morphology and histology. *Arthroscopy* 2010

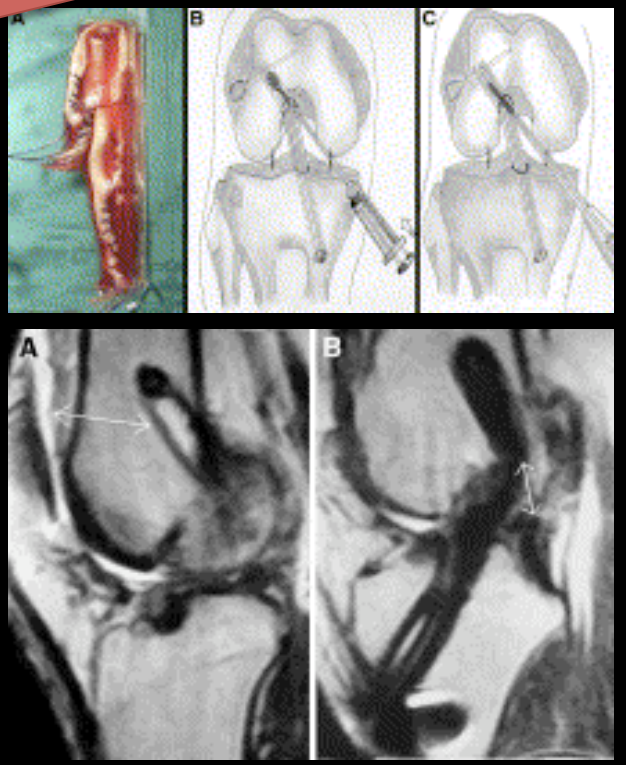
GF & MSCs

PRP

Graft maturation
Tunnel healing

Methods

- RCT, 108 patients
- Addition of platelet concentrate to a ST-gracilis graft and to the femoral tunnel



Results

- At 6 months FU
  - Higher rate ($P = 0.036$) of graft maturation (low-intensity signal on MRI)
  - No significant effect in osteoligamentous interface

Orrego et al. Effects of platelet concentrate and a bone plug on the healing of hamstring tendons in a bone tunnel. *Arthroscopy* 2008

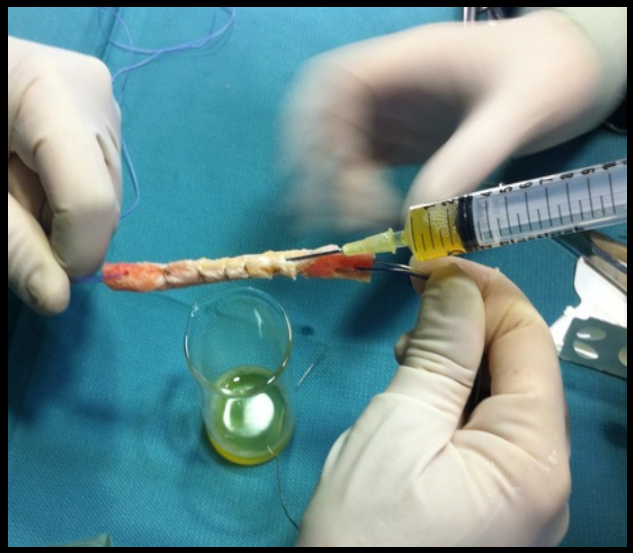
GF & MSCs

PRP

Donor-site Morbidity

Methods

- RCT, 40 patients
- Effect of the addition of autologous PRP gel sutured into the patellar and tibial bone plug harvest site



Results

- 12-month FU
  - VAS scores ➔ not significantly different
  - VISA scores (validated to quantify knee function in subjects with patellar tendinopathy)➔ significantly higher in patients treated with PRP $P = 0.041$

Usefulness of PRP in reducing subjective pain at the donor-site level

Cervellin et al. Autologous platelet- rich plasma gel to reduce donor-site morbidity after patellar tendon graft harvesting for ACL R: A randomized, controlled clinical study. *KSSTA* 2012

GF & MSCs

PRP

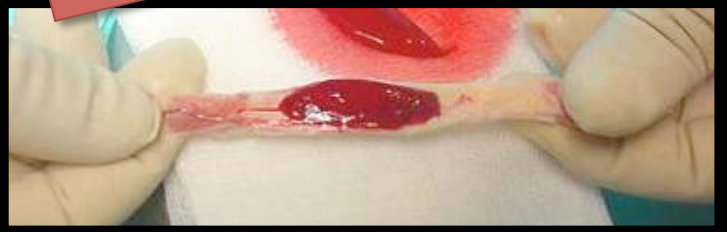
Purpose

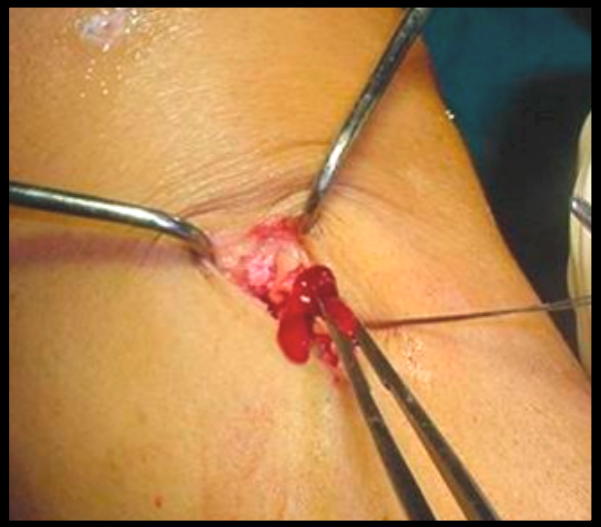
To evaluate the clinical and inflammatory parameters with the addition of platelet-derived growth factors (PDGF) in primary ACL R with B-PT-B allograft

Methods

- RCT, 100 patients
- Arthroscopic allograft ACL-R (n=50) vs a group in whom platelet-enriched gel was used (n=50)
- The platelet concentration was $837x10^3/mm^3$
- The gel was introduced inside the graft and in the tibial tunnel

Graft maturation
Tunnel healing





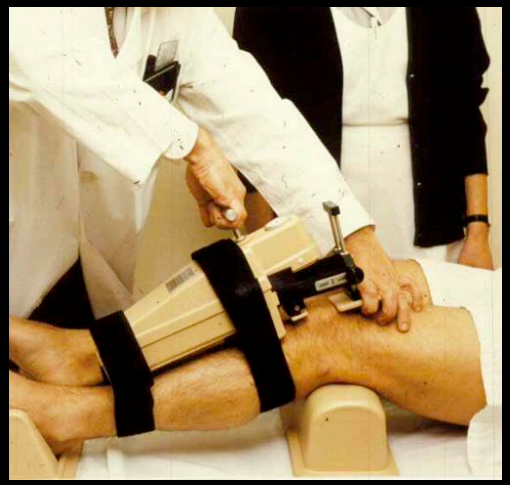
Valentí *Arthroscopy* 2009

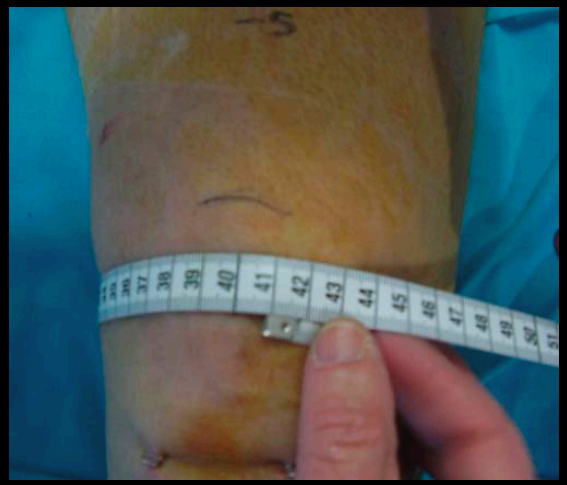
GF & MSCs

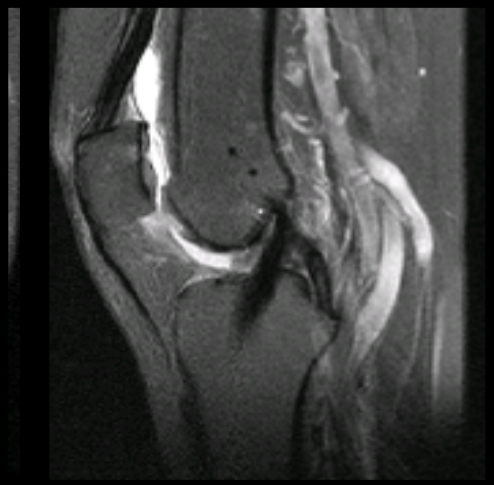
PRP

Results

- No differences in the number of associated injuries
- No statistically significant differences between the groups for
  - inflammatory parameters (knee perimeter and C-reactive protein level)
  - MR imaging appearance of the graft
  - clinical evaluation scores (VAS, IKDC, and KT-1000)





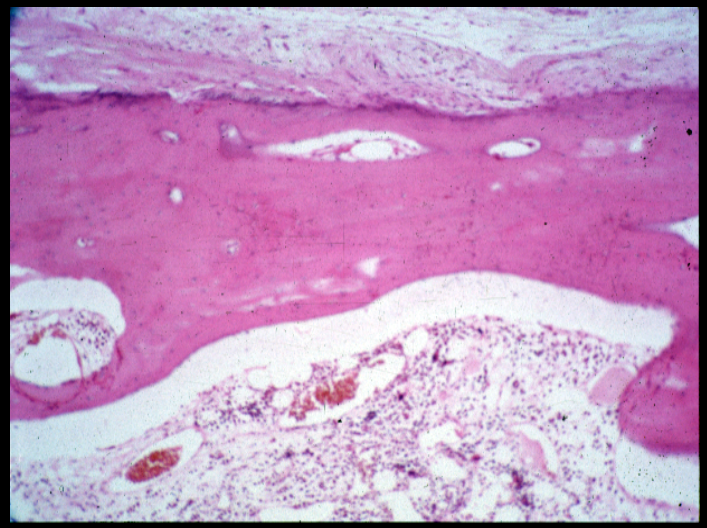


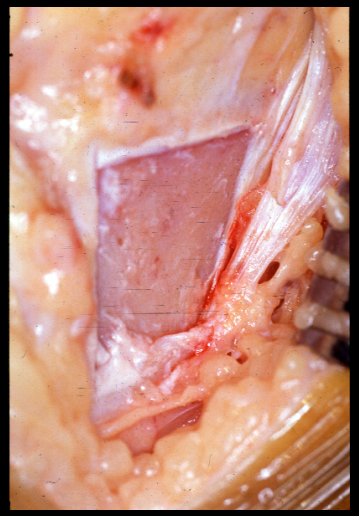
Valentí *Arthroscopy* 2009

Autografts

The Periosteum

- Periosteum consists of multipotent mesodermal cells
- It also contains chondroprogenitor and osteoprogenitor cells, which can form both cartilage and bone under appropriate conditions

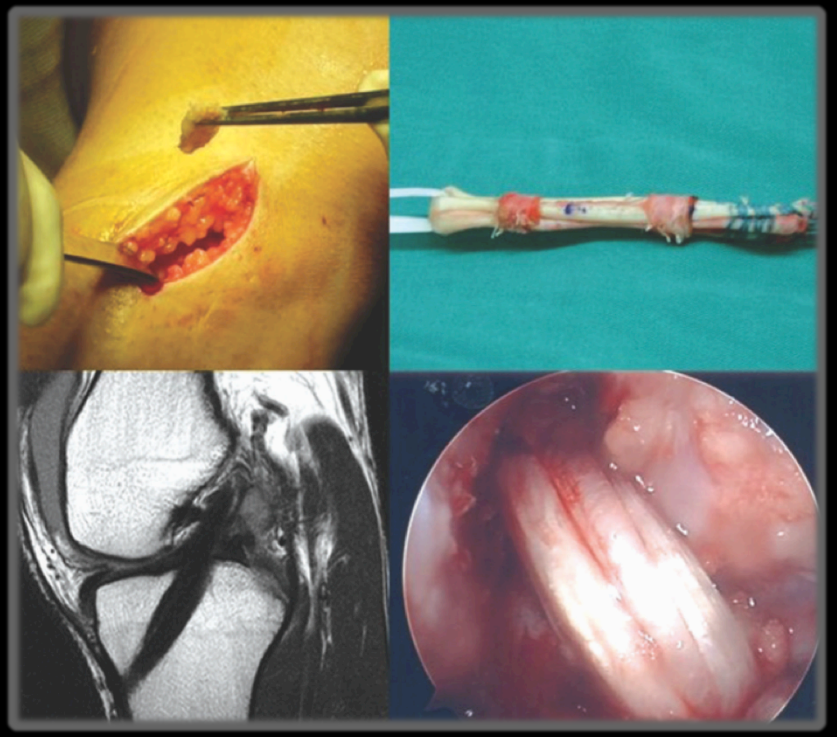




Periosteum-enveloping tendon graft

METHODS

- Double ST & gracilis graft (10 cm in length) with a periosteum flap wrapped (*cambium* layer placed outside)
- Case series → 368 pts
- From 2000 to 2005 / at least 2 y FU



RESULTS

- Minimal tunnel widening
  - 95% less than 1mm widening (both femur and tibia)

Chen *Arthroscopy* 2010

Biomaterials

The American Journal of Sports Medicine

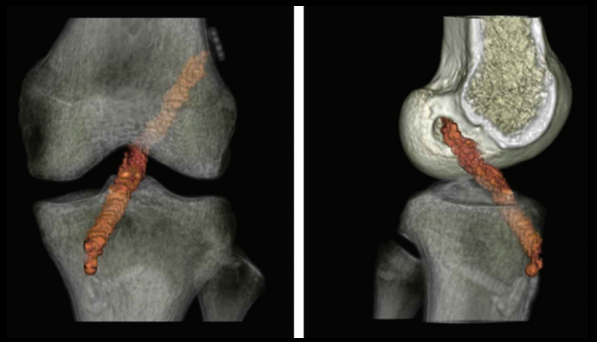
Effect of Calcium Phosphate–Hybridized Tendon Graft in Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial

Hirotaka Mutsuzaki, Akihiro Kanamori, Kotaro Ikeda, Shigeru Hioki, Tomonori Kinugasa and Masataka Sakane

Am J Sports Med 2012 40: 1772 originally published online June 19, 2012

Methods

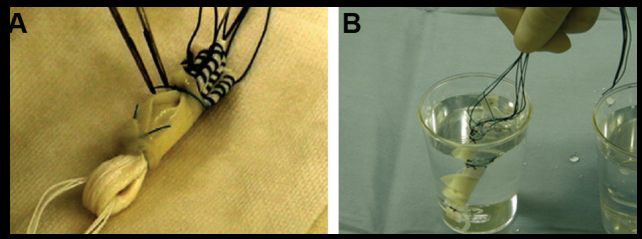
- RCT, n = 64 / wIth or w/out CaP (n = 32/32)
- TT Single-bundle ACL R 4-strand ST and gracilis / EndoButton femoral and screw washer tibial fixation

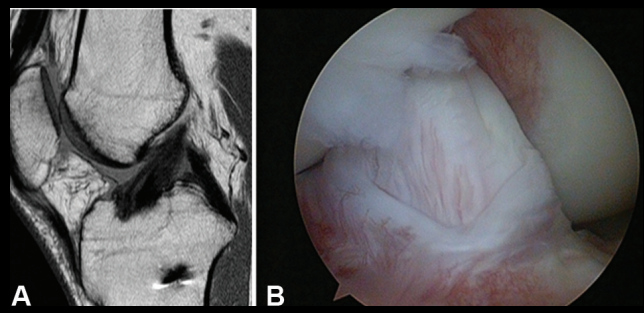


Results

Minimum 2-year FU

- Pivot-shift test, IKDC grade, and Tegner score; intensity of the tendon graft (MRI) and arthroscopic appearance not significantly different in the 2 groups
- CaP group
  - KT-1000 ➔significant decrease AP translation ($p < .05$)
  - Lysholm score higher ($p < .05$)
  - Reduced percentage of tunnel enlargement (AP diameter at the main joint aperture site in femoral & tibial side) $p < .05$

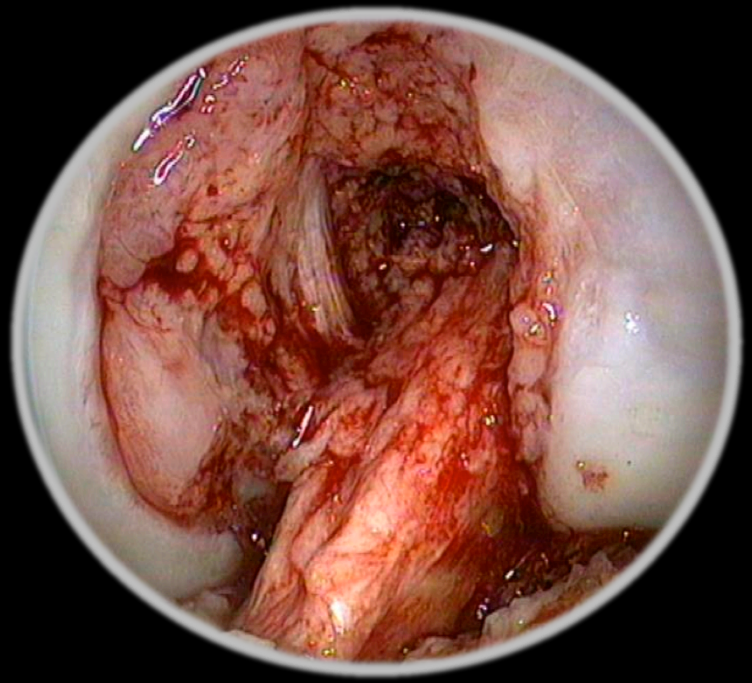


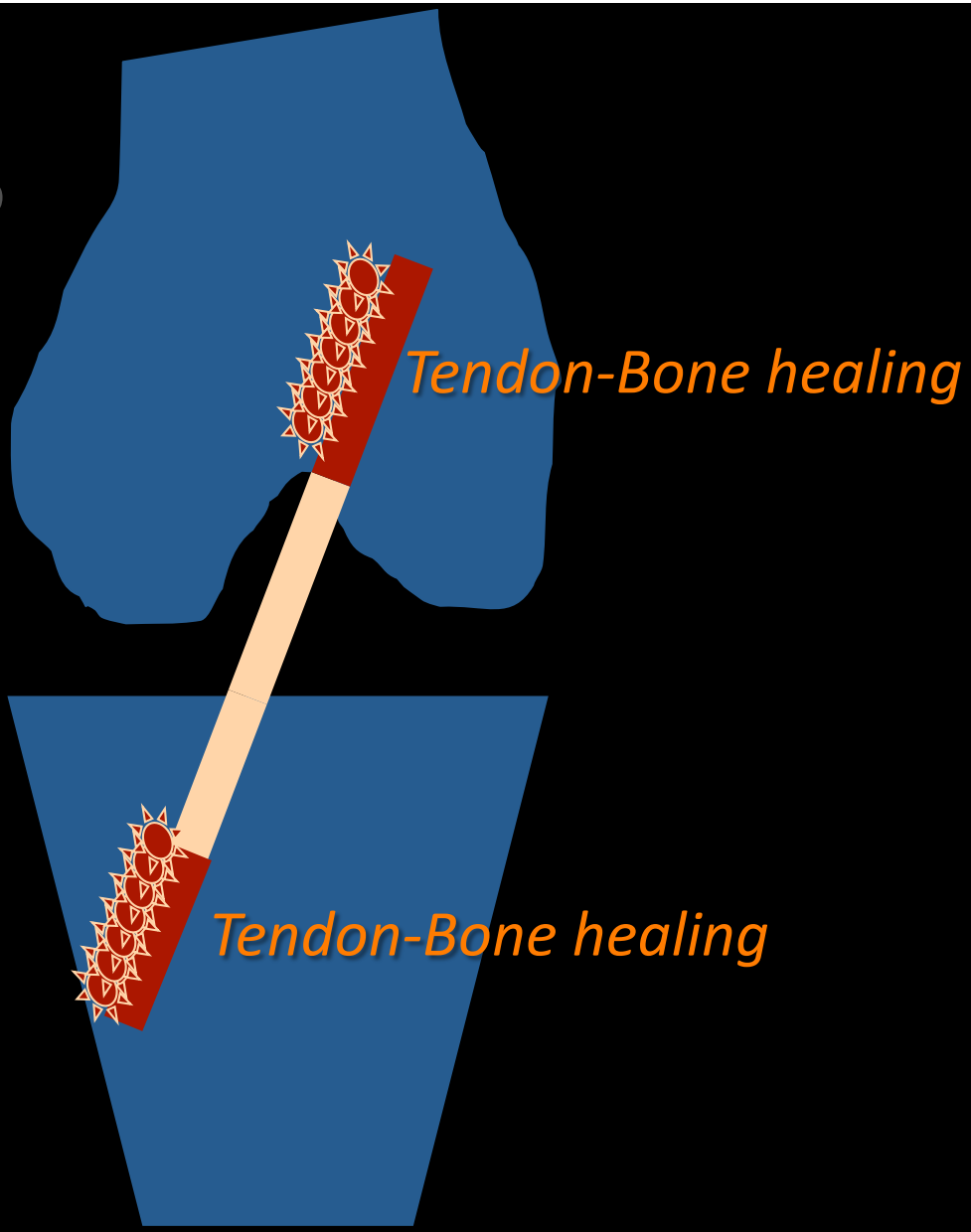


Future directions

- CITOKYNES → may provide important signals for tissue formation & differentiation
- GENE THERAPHY → may provide prolonged presence of important molecules for healing
- STEM CELLS → may provide a population of undifferentiated cells for healing
- TRANSCRIPTION FACTORS→ may direct nuclear gene expression

Clinical studies





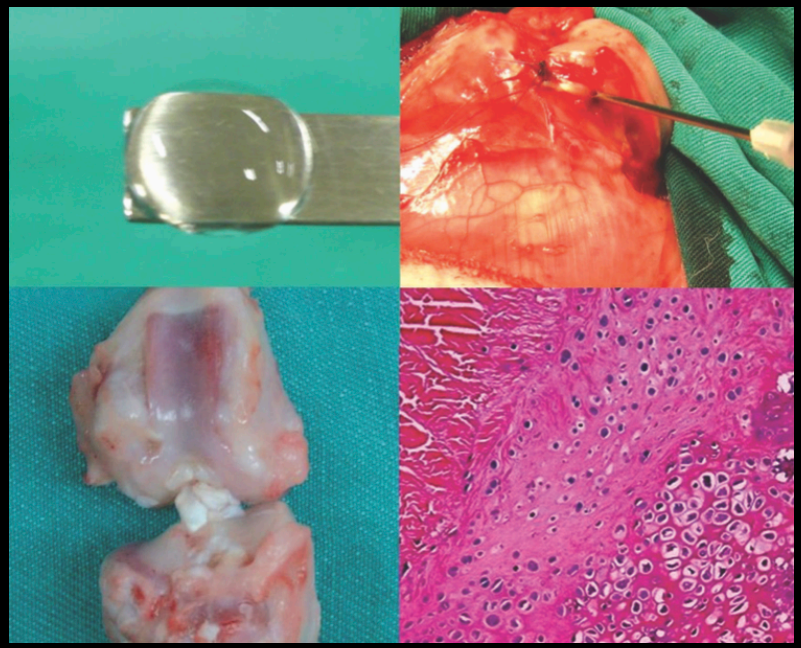
Experimental studies

Bone Marrow-Derived Mesenchymal Stem Cells Infected with BMP-2

GF & MSCs

Purpose

- New Zealand white rabbits
- Gastrocnemius tendons wrapped by bMSCs infected with the control virus (bMSCs+Lv-Control) vs gastrocnemius tendons wrapped by bMSCs infected with the recombinant BMP-2 virus (bMSCs+Lv-BMP-2)



Results

Week 4 to 8

- **Maximum loads** → significantly higher in bMSCs +Lv-BMP-2 group
- **Stiffness** → significantly higher in the bMSCs +Lv-BMP-2 group (32.5 ± 7.3 vs 22.8 ± 7.4)
- **Proliferation of cartilage-like cells** and formation of fibrocartilage-like tissue → highest within the bone tunnels in the bMSCs+Lv-BMP-2 group

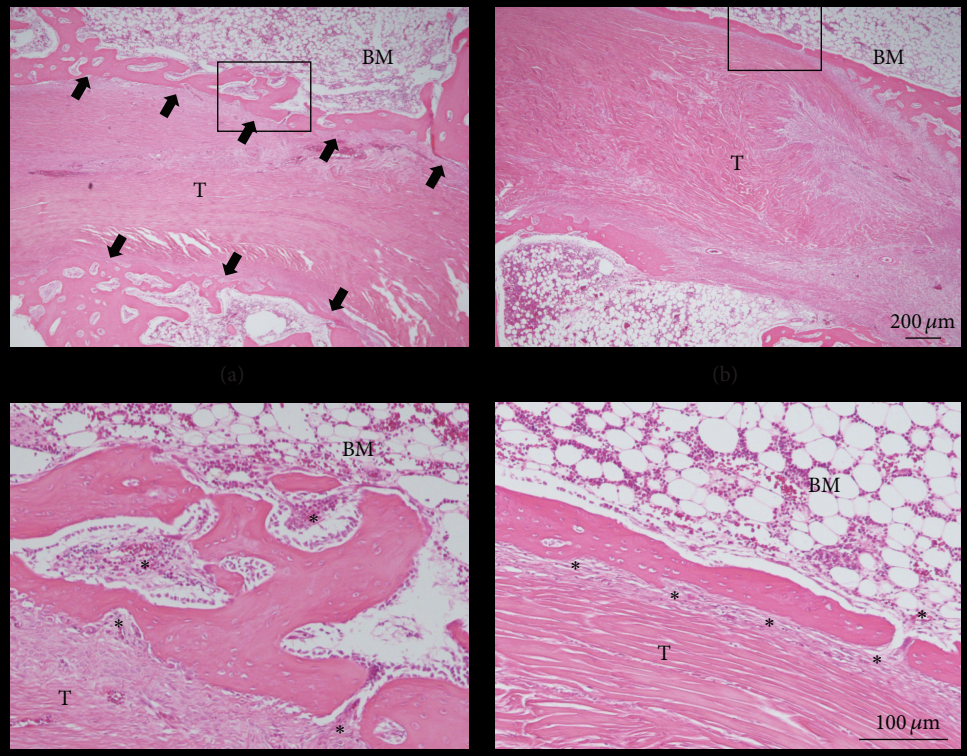
Dong 2012

Biomaterials

Osteogenic Matrix Cell Sheet Transplantation Enhances Early Tendon Graft to Bone Tunnel Healing in Rabbits

Yusuke Inagaki,[1] Kota Uematsu,[1] Manabu Akahane,[2] Yusuke Morita,[3] Munehiro Ogawa,[1] Tomoyuki Ueha,[1] Takamasa Shimizu,[1] Tomohiko Kura,[1] Kenji Kawate,[4] and Yasuhito Tanaka[1]

- To determine whether OMCS could induce bone formation around grafted tendons
- Skeletally mature Japanese white rabbits
- OMCS were transplanted into the interface between tendon and bone tunnel



RESULTS

- Newly formed bony walls and positive collagen type I staining were seen around the tendon with OMCS transplantation (thinner bony walls without)
- Bone volume ➔ signicantly higher in the OMCS transplantation group
- Pullout strength ➔ signicantly higher with OMCS (0.74 ± 0.23 N/mm2) than without

OMCS enhance early tendon to bone tunnel healing

Summary

- Improvement in graft-to-bone healing is crucial to ensure early aggressive RHB and early return to physical activities
- Several biological & physical agents to enhance the healing process of the tendon-bone interface have been evaluated in animal studies
- There is a lack of extensive clinical evaluation
- The current evidence shows a **very limited influence** of all this therapies on graft-bone interface healing and no significant difference in clinical outcomes

Take Home Message

- There is currently insufficient clinical evidence to support the routine use of these therapies for treating ACL injuries.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Pablo E. Gelber (Spain)
Thank you
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