6th Advanced Course on Knee Surgery
January 31st – February 5th, 2016 Val d'Isère - France

ACL ligamentization

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Financial disclosure

- No conflict of interest to disclose

Epidemiology

- 1 ACL reconstruction/2000 inhabitants in US
- 200’000 ACL reconstructions/year in US
- Direct cost $ 3 billions
- 120’000 TKR/year

Borphy et al *Am J Sports Med* 2009

- About 31’000 ACL reconstructions/year in France

Symposium *French Society of Arthroscopy* Paris 2008

- 3750-4000 ACL reconstructions/year in Switzerland

Graft remodeling

- Still a matter of debate

Biological process

- In animal models, the graft undergoes a process of adaptation rather than full restoration of the intact ACL's biological properties.

« Law of functional adaptation » Wilhem Roux

An organ will adapt itself structurally to an alteration, quantitatively and qualitatively in function

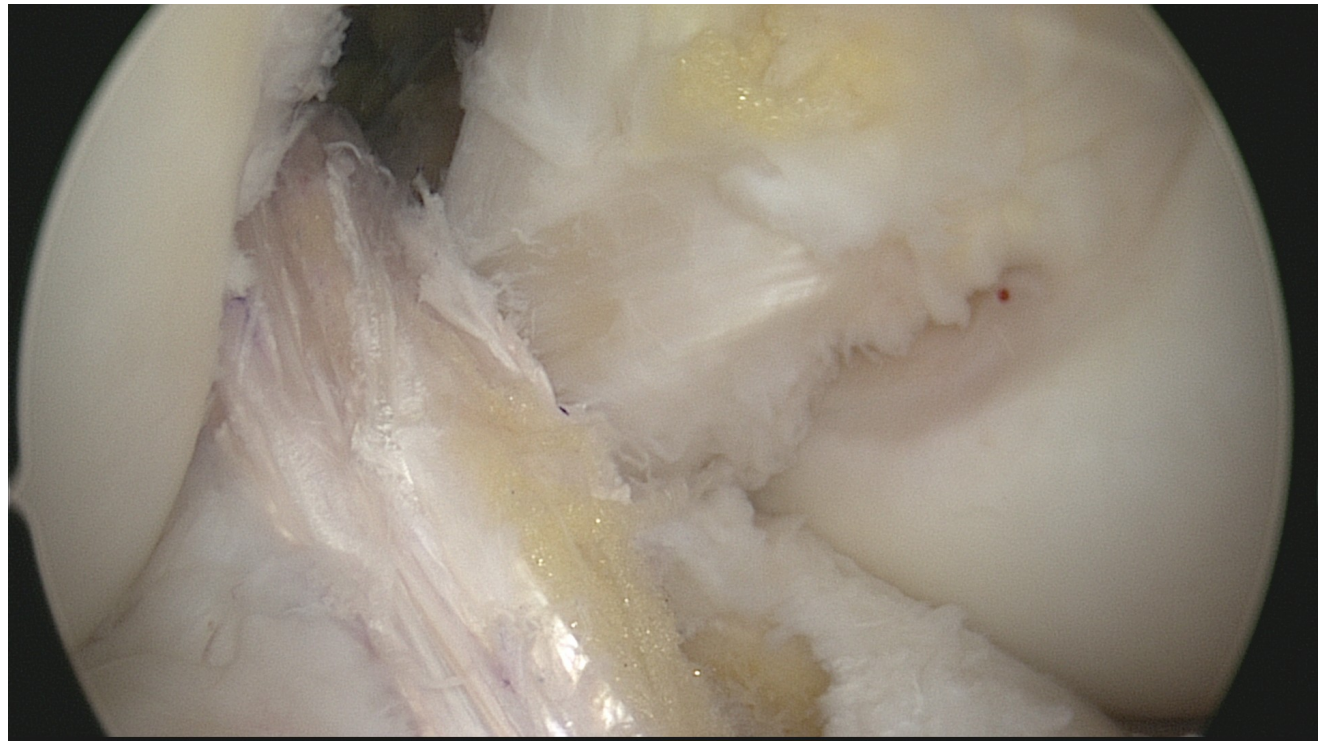
In human

- Same healing phases:
  - Graft necrosis, recellularisation, revascularization, ligamentization
- Remodeling is reduced
- Less necrosis (no more than 30%)
- Not all intrinsic grafts cells replaced by extrinsic cells
- Large area of normal collagen alignment and crimp pattern
- No excessive revascularization

Johnson *Arthroscopy* 1993
Rougraff et al *KSSTA* 1999

ACL graft in human

- V. H. basketball player 29 y old BPTB ACL-R



Ligamentisation

- V. H. basketball player 34 y old ACL BPTB, 5 years post-ACLrec

Even “two bundles”

- V. H. basketball player 34y old ACL BPTB, 5 years post-ACLrec

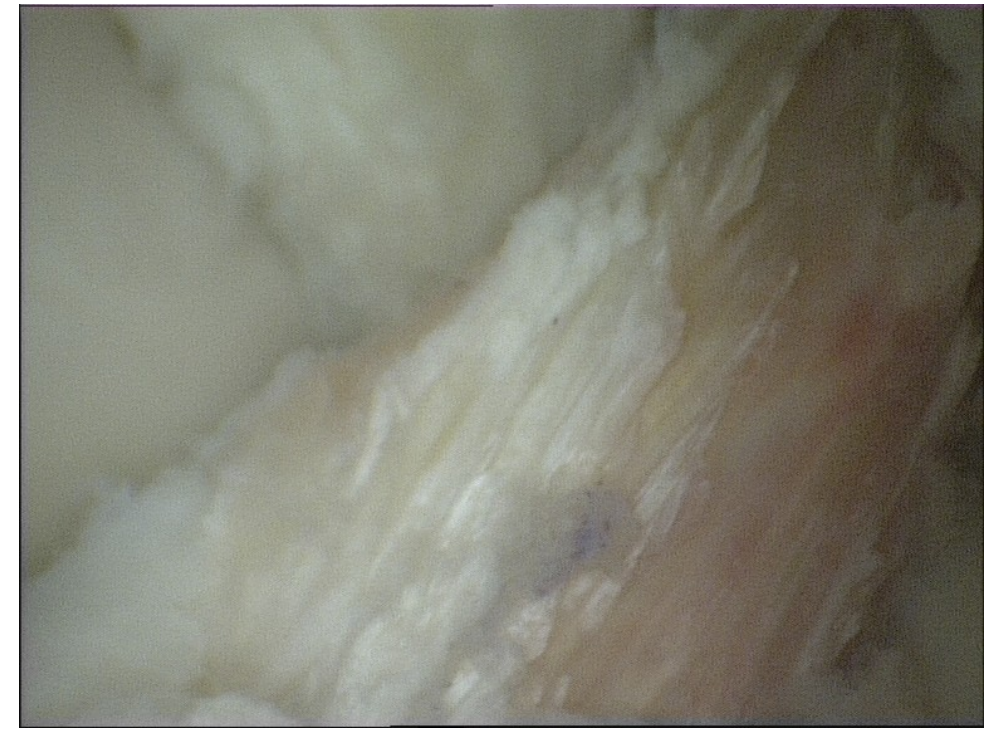
Basic science - Graft necrosis

- Released of cytokines
  - Matrix.-metalloproteinase (MMP-3)
  - Tissue inhibitor metalloproteinase-1 (TIMP)-1
  - Interleukin-6 and 8 (IL-6, IL-8)
  - Tumor necrosis factor alpha (TNF-a)
  - Il-1

Cameron et al *Am J Sports Med* 1997
Higuchi *Int Orthop* 2006

- Extended necrosis
- Collagen disturbance
- Myxoid degeneration
- Interfering process of revascularization

Basic science

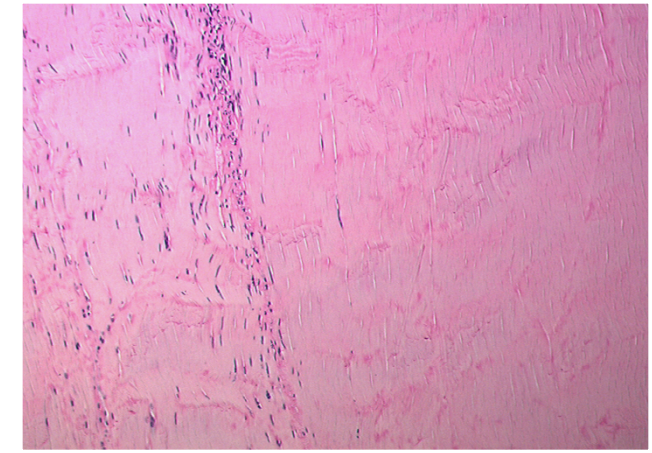


- Graft healing
  - Inflammatory phase (1-4th wk.)
  - Proliferative phase (4-12th wk.)
  - Ligamentization phase (12- …th wk.)

Amiel et al *J Orthop Res* 1986

Basic science

- Early healing phase
  - Central acellularity and necrosis
  - Influx of host cells
    - Inflammatory cells
    - Fibroblasts
  - Complete replacement of viable graft cells by hosts cells around 2-4 weeks in animal models



Kleiner et al *J Orthop Res* 1986
Kobayashi et al *Trans Orthop Res* 2005

  - No revascularization

Basic science

- Proliferation phase (4-12 wks)

  - Increased cellularity with proliferation of fibroblast – myofibroblasts
  - Loss and reformation of collagen crimp
  - Revascularization

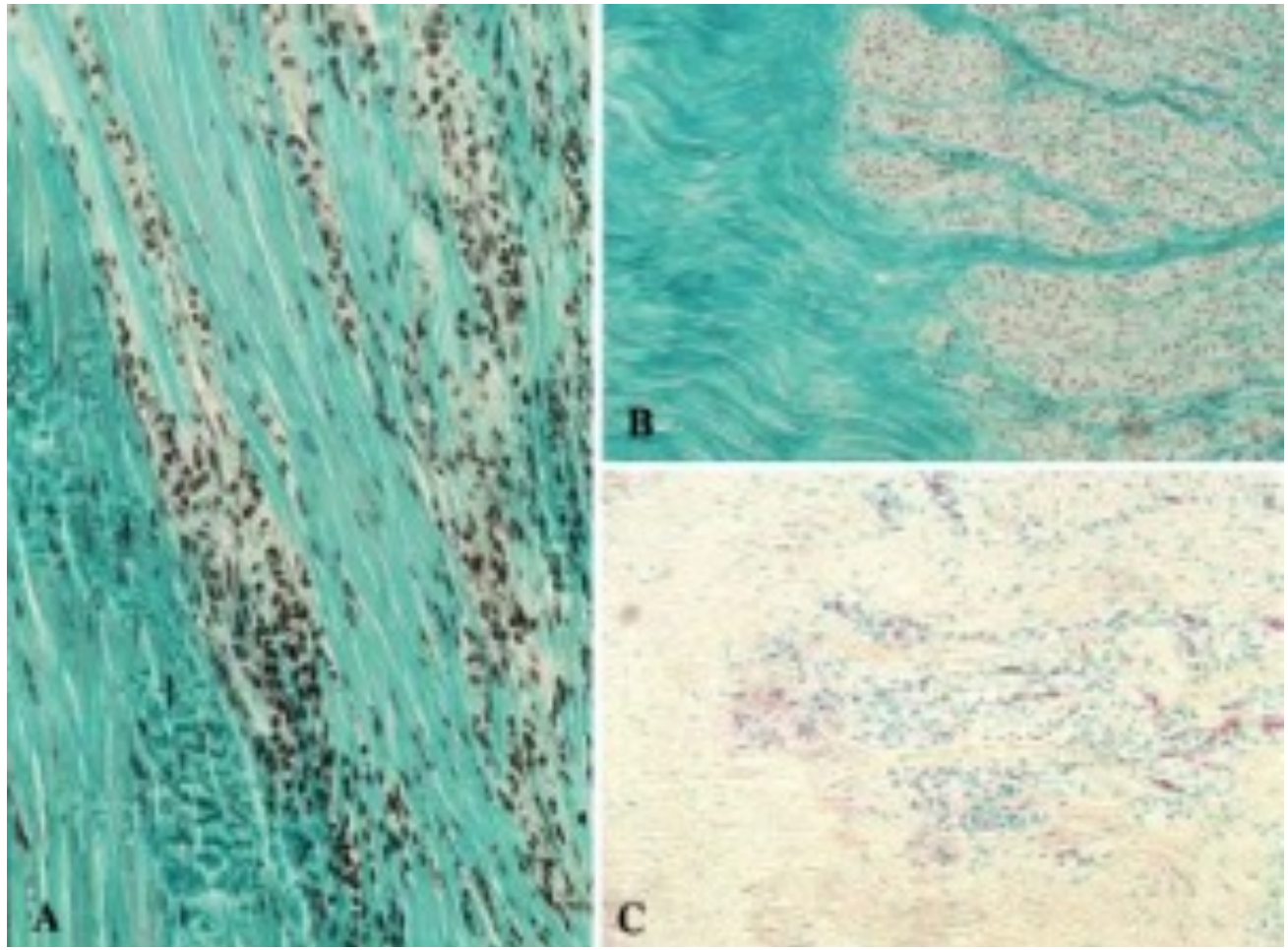
  proliferative

  - Increased collagen type III / fibronectin
  - Increase smaller diameter collagen fibrils
  - Increased GAG content

  reparative

Basic science proliferation phase (4-12th wks)

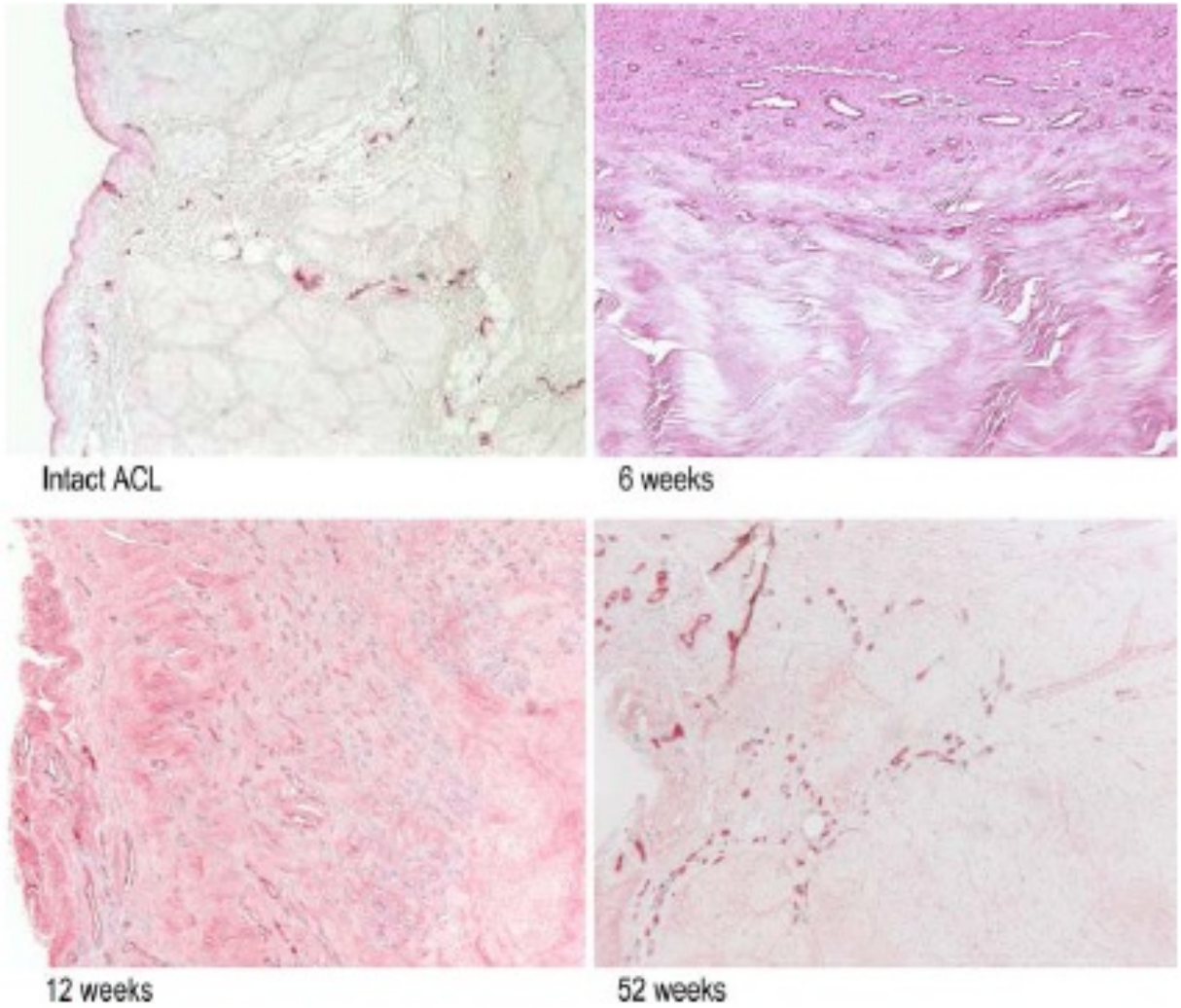
- Recellularization (4-12 wks)



Scheffler et al *Knee Surg Sports Traumatol Arthrosc* 2008

Basic science proliferation phase (4-12th wks)

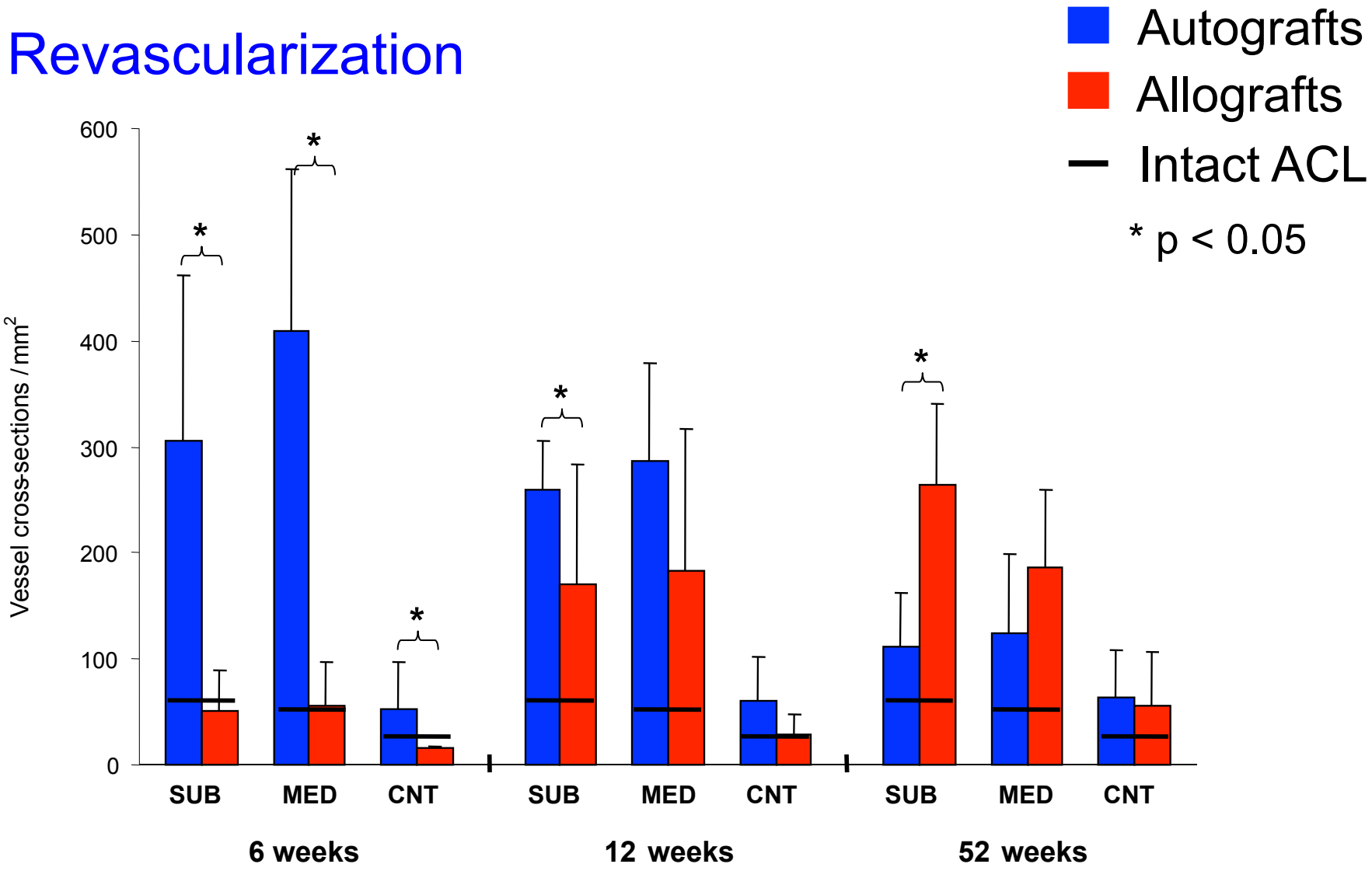
- Revascularization (4-12 wks)



Scheffler et al *Knee Surg Sports Traumatol Arthrosc* 2008

Basic science: Proliferation phase (4-12 wks)

- Revascularization



Courtesy of Scheffler et al., Arthroscopy, Richard O`Conner Award 2007

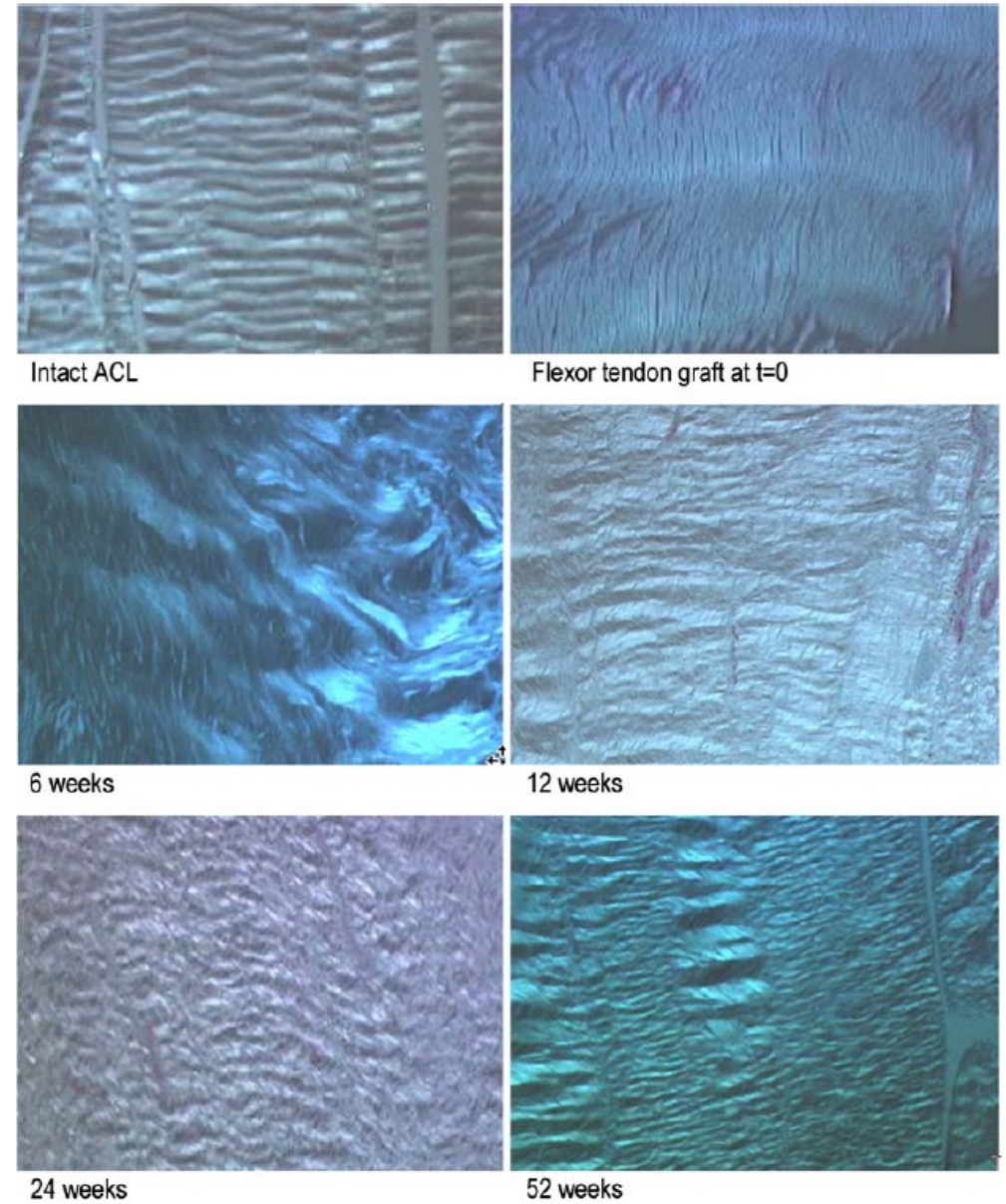
Basic science

- Ligamentization phase (12-… wks)
  - Remodeling phase:
    - Structural and mechanical adaptation
    - Increased in collagen content
    - Non-reducible/reducible cross-link ratio increase

Maeda et al *Clin Orthop Res* 1997
Jackson et al *Am J Sports Med* 1993
Kirkpatrick et al *J South Orthop Assoc* 1996
Nikolaou et al *Am J Sports Med* 1986
Arnoczky et al *J Bone Joint Surg* 1986
Shino et al *J Bone Joint Surg* 1984
Scheffler et al *Arthroscopy* 2008

Original ACL versus graft

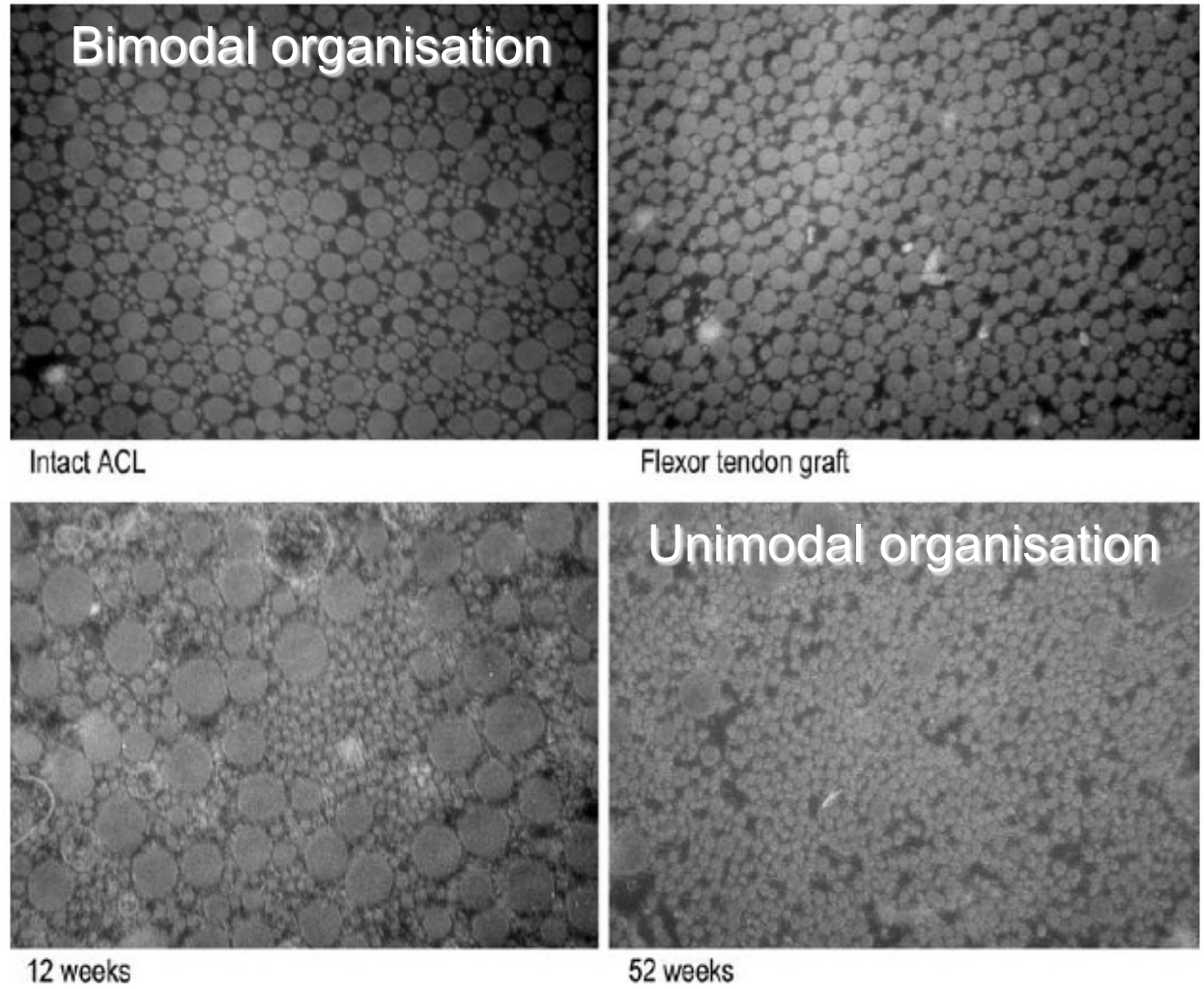
- Collagen crimp pattern a sheep model
- Polarized light microscopy x200



Scheffler et al *Knee Surg Sports Traumatol Arthrosc* 2008

Original ACL versus graft

- Collagen remodeling sheep model



Scheffler et al *Knee Surg Sports Traumatol Arthrosc* 2008

Original ACL versus graft

- Similar macro-morphology within 6 to 12 months
- More type III collagen in the graft
- Unimodal pattern of small collagen fibers
- Crimp frequency remain increased in the graft
- In animal model, graft strength could never surpass 50-60% of the intact ACL

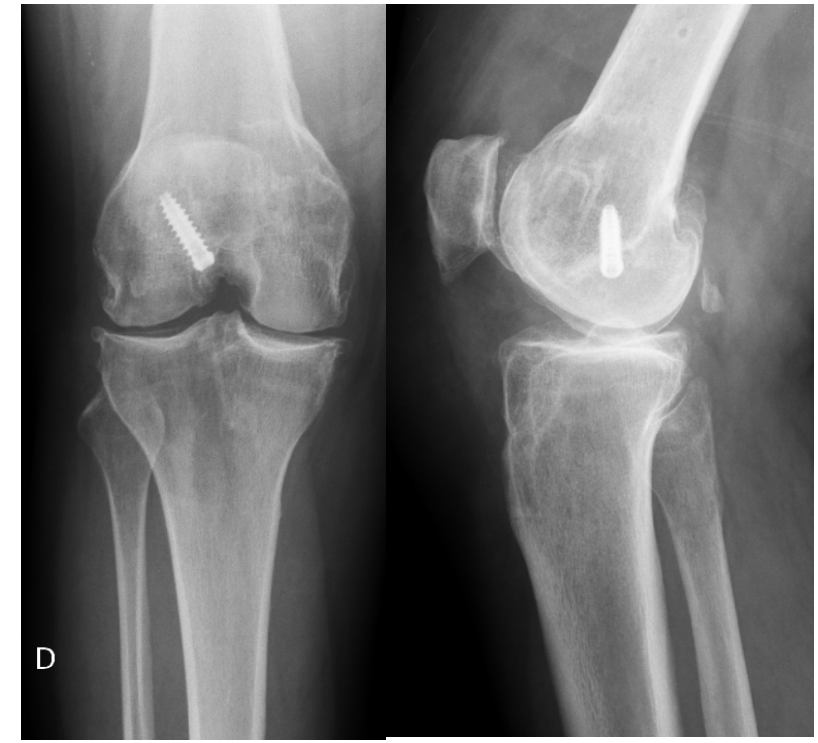
Abe et al Arthroscopy 1993
Jackson Am J Sports Med 1993
Liu et al CORR 1995
Weiler et al J Orthop Res 2002
Weiler et al Am j Sports Med 2004
Scheffler et al KSSTA 2008

In summary

- The ligamentization process is an adaptative tranformation of the graft which does not lead to a full restoration of the intact ACL's biological properties.

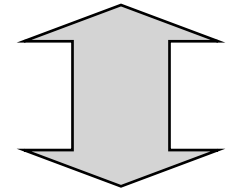
What we know !

- MECHANICAL ENVIRONMENT
  - Placement of the graft
  - Tensioning
  - Rehabilitation
  - Patient compliance
  - It takes time…



Biology - biomechanics

- To carry out a good biology



- No overloading of the graft

Overtensioning an ACL graft may adversely affect its biologic incorporation

Yoshiya et al *Am J Sports Med* 1987

Vascularization

- Overtensioning of the graft
- Patients habits:
    - Smoking, cocaine consumption
- Diabetes
- Choice of the graft
- Hypoxia
    - Period of avascular necrosis – decrease in VEGF expression

Cells repopulation

- Vascularization
- GF cascade: TGF-b_1, b-FGF, PDGF
- Age ?
- Genetic background ?
  - Fast healer ?
  - Slow healer ?

Kuroda et al *KSSTA* 2000

Matrix remodeling

- GF cascade: TGF-b_1, b-FGF, PDGF
- Vascularization
- Cell repopulation
- Age ?
- Genetic background ?
    - Fast healer ?
    - Slow healer ?

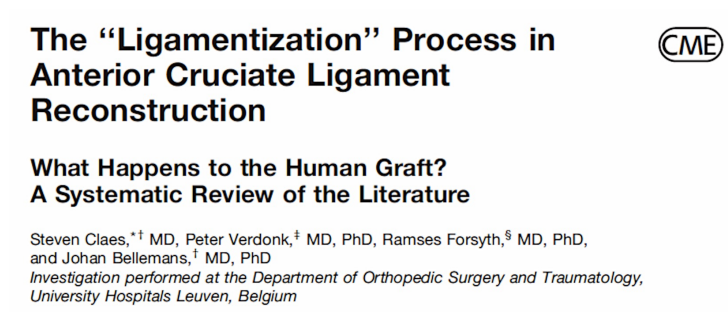
Kuroda et al *KSSTA* 2000

Ligamentization

- Patient's dependent
- Biological environment (smoking, cocaine, ectasy, diabetes)
- Mechanical environment
  - Placement of the graft
  - Tensioning
- Post-op rehabilitation

Menetrey et al *KSSTA* 2008

What we know today in human


The "Ligamentization" Process in Anterior Cruciate Ligament Reconstruction

CME

What Happens to the Human Graft?
A Systematic Review of the Literature

Steven Claes,*† MD, Peter Verdonk,‡ MD, PhD, Ramses Forsyth,§ MD, PhD, and Johan Bellemans,† MD, PhD
Investigation performed at the Department of Orthopedic Surgery and Traumatology, University Hospitals Leuven, Belgium

- ✓ 4 studies with biopsies of human grafts after different time periods
- ✓ A free tendon graft can be sufficiently biologically converted into a ligament - "Ligamentization."
- ✓ Human graft is not going to be necrotic (Difference in comparison to animal studies)
- ✓ Histologically: After "ligamentization process" the graft shows similar structure in comparison to the original ACL (with ultrastructural differences)
- ✓ Different periods of converting process have been reported but there is no consensus of a distinguished time period of this process!

Claes et al *Am J Sports Med* 2011

What we know in 2016

The "Ligamentization" Process in Anterior Cruciate Ligament Reconstruction

CME

What Happens to the Human Graft? A Systematic Review of the Literature

Steven Claes,*† MD, Peter Verdonk,‡ MD, PhD, Ramses Forsyth,§ MD, PhD, and Johan Bellemans,† MD, PhD
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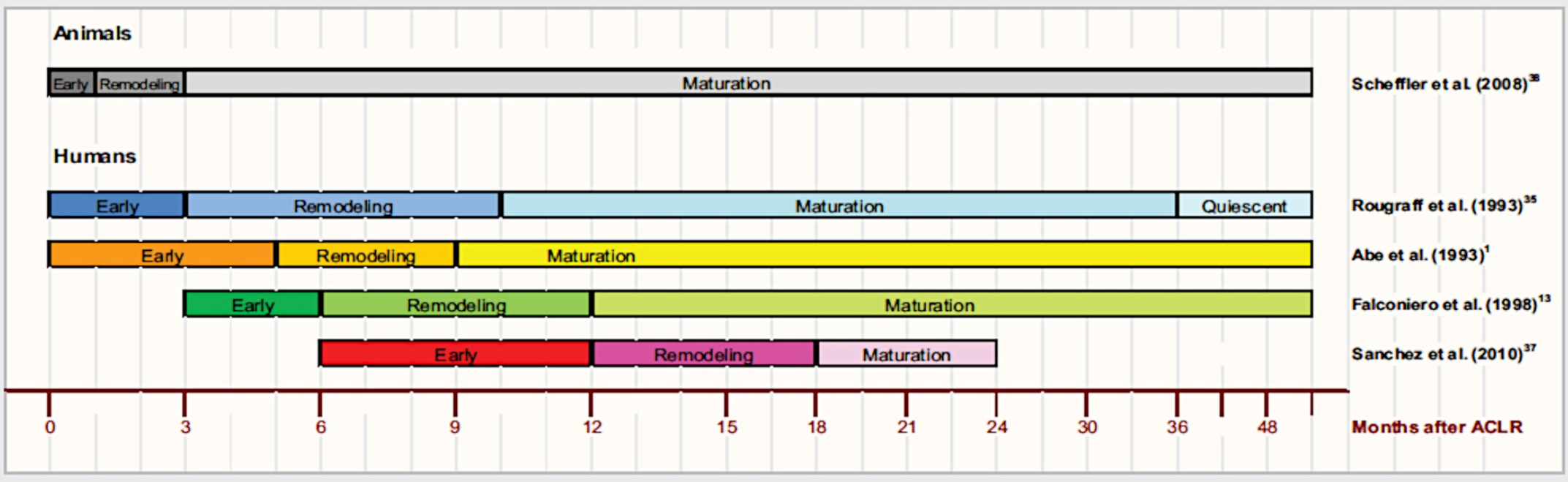


- After 6 months (minimum) sufficient ligament properties can be expected
- No information about core biopsies....!

Claes et al *Am J Sports Med* 2011

Skeletal Radiol (2013) 42:541–552
DOI 10.1007/s00256-012-1534-y

SCIENTIFIC ARTICLE

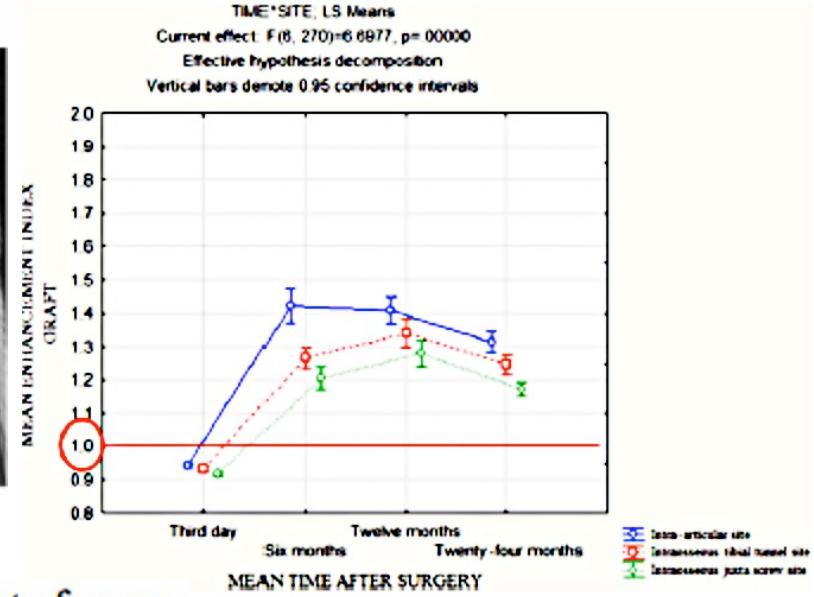
Evaluation with contrast-enhanced magnetic resonance imaging of the anterior cruciate ligament graft during its healing process: a two-year prospective study

Aikaterini Ntoulia · Frederica Papadopoulou · Franceska Zampeli · Stavros Ristanis · Maria Argyropoulou · Anastasios Georgoulis

6 months

12 months

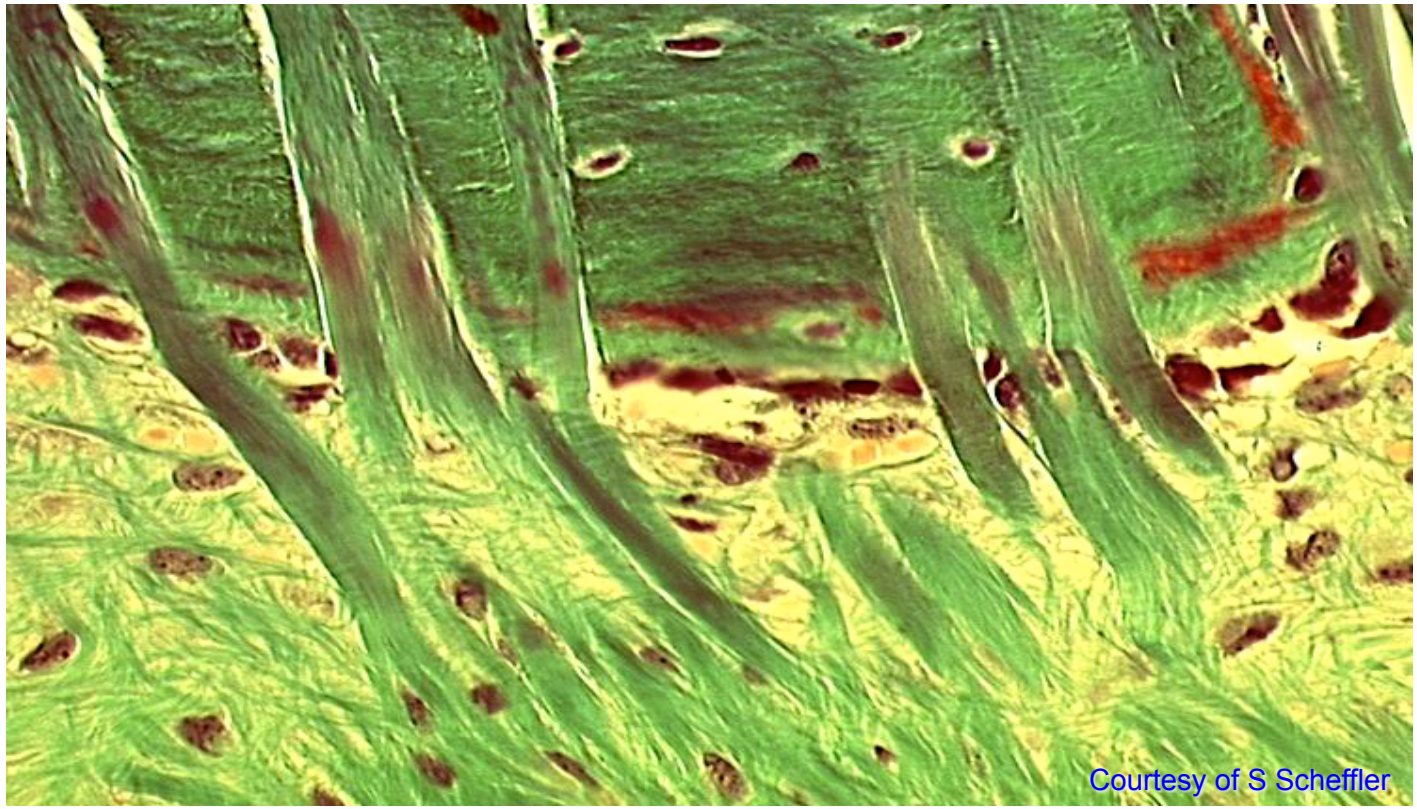
24 months



Conclusion During the healing process the amount of revascularization tissue influences the MR imaging characteristics of the graft according to the examined site and the time interval after surgery. By 2 years postoperatively, revascularization completion coincides with the homogeneously low signal intensity of the graft, closely resembling native ACL.

Tunnel healing

- Bone-to-bone healing
- Tendon-bone healing



Tendon-to-bone healing

- Three factors to explain ineffective healing:
  - Presence of persistent inflammation
  - Tendon-bone interface motion
  - Insufficient number of undifferentiated cells

Steiner et al *Am J Sports Med* 2008

Role of inflammation

- Macrophages depletion:
  - Rat model
  - Reduced fibro-vascular scar
  - Enhanced bone ingrowth
  - Improved collagen continuity between bone and tendon
- NSAIDs delay ligament healing

Hays et al *JBJS* 2009
Warden et al *Am J Sports Med* 2006

Tendon-to-bone micromotion

- Inverse correlation between motion and healing in the femoral tunnel

- Graft tunnel motion may impair early graft incorporation and may lead to osteoclast-mediated bone resorption

Rodeo et al *JBJS* 2003
Rodeo et al *Am J Sports Med* 2006

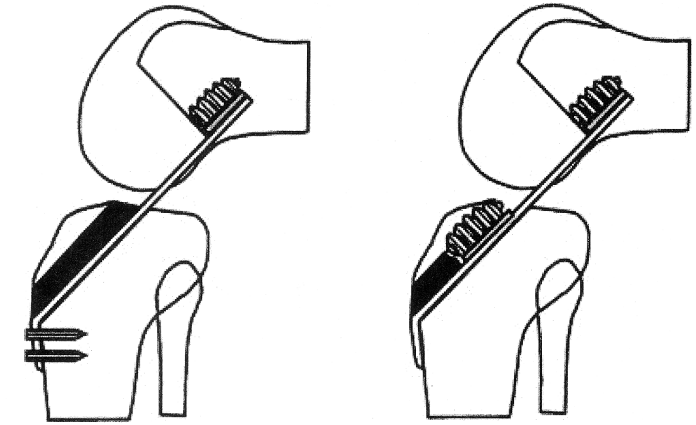
- No "aggressive" or accelerated rehabilitation
- Immobilization?

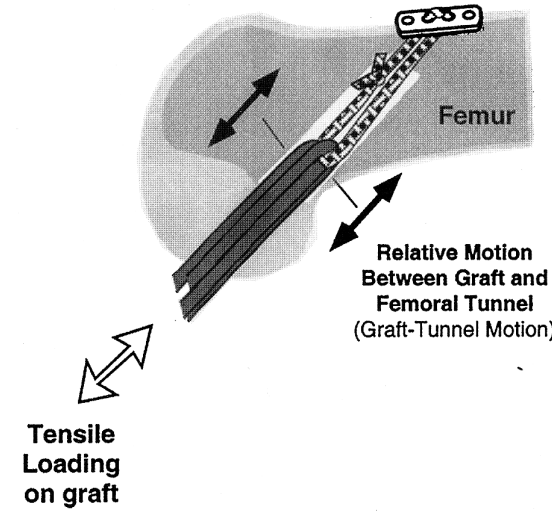
Fixation

TABLE 2
Ultimate Tensile Load of Various Fixation Devices[a]

Type of fixation device	Ultimate tensile load (N)	Ref.
Indirect		
Single polyester tape loop	375 ± 8	104
Double polyester tape loop	612–651	84, 104
Single loop 5 Ethibond	238 ± 3	104
Double loop 5 Ethibond	463 ± 18	104
Direct soft tissue		
Metal interference screw (7 mm)	242 ± 90	20
Bioabsorbable screw (7 mm)	341 ± 163	20
Bone mulch screw	1126 ± 80	72
Tandem soft tissue washers	768	72
Cross-pin technique (animal)	725–1600	22
Suture-post (animal)	374	78
Direct bone		
Metal interference screw (7 mm)	640 ± 201	81
Metal interference screw (9 mm)	276–436	59, 75
Metal interference screw (11 mm)	302	75
Metal interference screw (13 mm)	328	75
Metal interference screw (15 mm)	328	75
Bioabsorbable screw (7 mm)	330–418	81
Bioabsorbable screw (9 mm)	565	59
Staples	588	32

[a] Experiments were performed on human cadaveric knees unless specified.





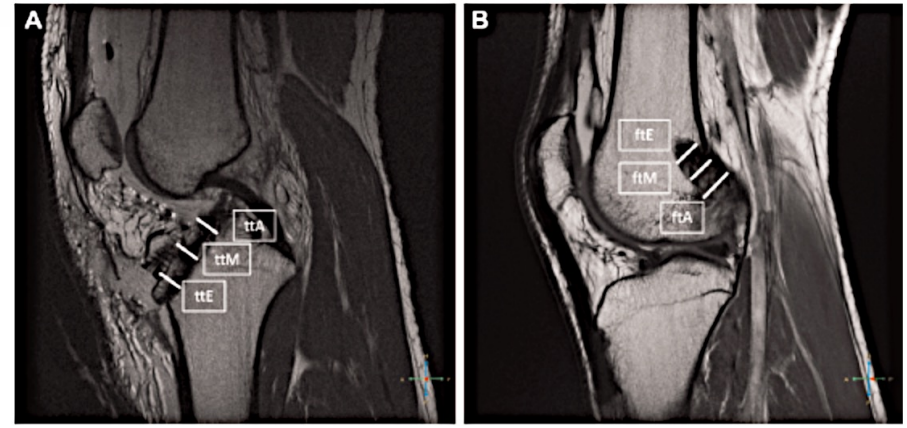
Ishibashi et al *Am J Sports Med* 1996
Fu et al *Am J Sports Med* 1999

Tibial and Femoral Tunnel Changes After ACL Reconstruction

A Prospective 2-Year Longitudinal MRI Study

Alexander E. Weber,* MD, Demetris Delos,† MD, Hanna N. Oltean,* MPH,
Katherine Vadasdi,† MD, John Cavanaugh,‡ PT, MEd, ATC, SCS,
Hollis G. Potter,§ MD, and Scott A. Rodeo,†‖ MD
Investigation performed at the Hospital for Special Surgery, New York, New York, USA

- n=18
- MRI at T0, 6, 12, 24, 52, 104 weeks
- Look at the tunnel CSA



- Tunnel expansion occurs early (0-6 w) and at tunnel aperture
- Younger age, male sex and time between injury and reconstruction (>1 year) were strong predictors of tunnel expansion

Weber et al *Am J Sports Med* 2015

In summary

- Better understanding of healing processes
- Ligamentization does occur in human ACL
- Beware of the use of NSAIDs
- Patient’s profile
- Rehab protocol
- It may take time…

European Society of Sports Traumatology, Knee Surgery & Arthroscopy

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17th ESSKA Congress

4 - 7 May 2016

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Thank you for listening

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