Target audience: Radiologists and imaging scientists interested in assessing cartilage repair, including the use of quantitative techniques to assess repair tissue biochemistry.

Outcome/Objectives:
1. To become familiar with different appearance of cartilage repair techniques
2. To become familiar with both morphologic and quantitative assessment of repair

Purpose: Articular cartilage has little to no inherent capacity for self-repair. The presentation will outline both scaffold and cell-based repair techniques, demonstrating both surgical approach and both early and longer term MR appearance of the repair tissue.

Methods and Results: Review of pertinent literature of MRI of cartilage repair

Articular Cartilage has little to no capacity to undergo spontaneous repair
- avascular; unable to regenerate across a physical gap

Marrow stimulation (microfracture +/- augmentation)

Osteochondral transfer
- autologous (mosaicplasty; OATS, AOT)
- allograft (fresh cadaveric tissue)

Tissue Engineered Cartilage (three requirements)
- matrix scaffold to support tissue formation → chemical composition and physical structure attract endogenous cells (“cell homing”)
  - carbohydrate based polymers (polylactic acid)
  - protein based polymers (collagen, fibrin)
- cells
  - chondrocytes
  - chondroprogenitor cell pools (cambial layer of periosteum and perichondrium)
  - mesenchymal stem cells from the bone marrow or synovial membrane
- signaling molecules (cytokines): PRP, FGF18 appear promising
  - Signaling by fibroblast growth factor (FGF) 18 promotes chondrocyte proliferation and differentiation

Works through activation of FGF receptor 3 (Moore et al; OA & Cart 2005)

MRI as Primary Outcome Measure: Cartilage Repair

- Signal intensity of tissue (ROI)
- Integrity/hypertrophy of periosteal flap
- Morphology: presence/absence of displacement (ACI/ OCA)
- Interface with native cartilage
- Volume of repair “fill”
- Appearance/morphology of subchondral bone
- Assess adj./opp. articular cartilage
- Presence/absence of inflammatory synovitis
- MR observation of cartilage repair tissue (MOCART)
  Marlovits et al; Eur J Radiol 2006; 57:16-23
  - Correlated to KOOS and VAS; significant correlation for fill, structure, subchondral bone, SI
  - ICC (3 readers); κ range: 0.765-1.00

Imaging of Cartilage Structure
- Water proton pools:
  - Free water (accounts for bulk of MRI signal)
  - Bound to PG by electrostatic charge (assess fixed charge density)
    - Sodium MRI
• GAG CEST
• Gd-DTPA² techniques (dGEMRIC)
  • T1 rho imaging
• Associated with collagen fibrils
• Quantitative T2 mapping:
  • Assess alterations in collagen orientation
• Diffusion tensor weighted imaging

Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques

*Minas et al, AJSM 2009*
- 321 patients treated with autologous chondrocyte implantation
- Prior marrow stimulation: 26% failures (29/111)
- No prior marrow stimulation: 8% failures (17/214)

Imaging of Microfracture
*Prospective study of 48 patients treated with microfracture evaluated by validated clinical outcome instruments and cartilage sensitive MRI*
- Bony overgrowth was noted in 25% of patients, but did not have a negative effect on clinical outcome scores
- Adverse functional scores after 24 months did correlate with poor percentage fill

*J Bone Joint Surg 2005; 87(9):1911-1920*

24 year-old professional football player with unstable lesion MFC

Preop 4/05 4 months post microfracture 8/05
- Welsch et al (*Radiology 2008; 247:154-161*) studied 20 pts following MFX or MACT with mean F/U 28.6 vs 27.4 mo
- MFX tissue showed reduced mean T2 whereas MACT showed mean T2 similar to control tissue (56.4msec); MFX showed no stratification while MACT did from deep to superficial areas

Cell-Based Approaches for Cartilage Repair
- Cell-based approaches hold great promise but there are still limitations to overcome
- Just adding pluripotent cells and hoping something good will happen may not be enough!
- Implanted cells need appropriate signals to drive differentiation
- The composition (specific matrix proteins) is often made by the cells but the structure of hyaline cartilage is not completely reformed

Matrix-Induced Autologous Chondrocyte Implantation (MACI)
- 3D scaffold supports maintenance of chondrocyte phenotype in culture
- Also serves as delivery vehicle for cells
- Autologous cells seeded on a hyaluronic acid or collagen scaffold
- Implantation approximately 4 weeks later
- Reduced technical complexity
  - No periosteum harvest
  - No suturing
  - Fibrin glue fixation
  - Arthroscopic implantation
- Used since 2001 in Europe & Australia
• Significant limitation of cell-based techniques is de-differentiation of cells in culture → variable expression of cartilage-forming genes
  - Chondroselect™ technique (Tigenix, Inc.) selects a subset of cells that express chondrocyte phenotype in culture

Tissue Engineering Strategies
• Paradigm: cells + scaffold + cytokines + mechanical stimulation
• NeoCart (Histogenics, Waltham, MA)
• Cartilage biopsy → Chondrocytes expanded in culture
• Cells then seeded on a bovine type-I collagen 3-D honeycomb matrix
• Culture in bioreactor – hydrostatic pressure controlled
• Bioreactor conditions support chondrocyte phenotype
• Average implant development time 67 days

Tissue Transplantation
• Direct implantation of osteochondral tissue with hyaline cartilage
• Indications: Osteochondral defect - bone loss
• Allows restoration of architecture/geometry
• Autograft OATS: lesion size under 15mm diameter
  - Limitation: donor site morbidity
• Allograft OATS for larger lesions
  - Limitation: tissue availability
  • fresh tissue requires immediate transplantation

Imaging of Osteochondral Allografts
◆ Prospective, longitudinal study of cartilage defects treated with hypothermically stored fresh osteochondral allografts using validated clinical outcome instruments and MRI
◆ Allografts remain intact without displacement
  - fissures noted at the graft/host interspace in 14/18 (78%) grafts
  - poor incorporation was noted in 4/18 (22%) grafts, 1 had intense bone marrow edema pattern and 3 had frank subchondral marrow fibrosis (low signal on all pulse sequences)
  - collapse of the subchondral bone in the graft was correlated to lack of bony integration based on signal characteristics
• Sirlin et al. correlated MRI of shell osteochondral allografts to the results of antihuman leukocyte antigen antibody screening (Radiology 2001;219:35-43)
  - Pts. who expressed positive humoral immune responses were associated with decreased incorporation, greater marrow edema pattern and a higher proportion of surface collapse of their graft


Juvenile Articular Cartilage Allograft
DeNovo NT Graft (Natural Tissue Graft®)
• Minced cartilage derived from juvenile human donors (allograft)
• There is a dramatic age-related decline in human chondrocyte chondrogenic potential
• Juvenile tissue has much higher proliferative capacity
• The material is suspended in fibrin glue and attached to lesion site using fibrin glue
Quantitative MRI: Issues of Data Acquisition

- Ideally assess both PG and collagen
- Clinical trial challenges for reproducibility: QMRI
  - Add to scan time!!
  - Software availability
  - Magnetic field strength (Na$^{23}$, T1rho)
  - Contrast agents (dGEMRIC)
  - Magic angle prolongation (T2, T1rho)
  - Coil choice (Na$^{23}$)
  - Parameters of acquisition (SNR, resolution, # echoes)
  - Post-processing algorithm (2 vs. 3 parameter fit)
  - Registration software


MRI of cartilage repair

- Future repair strategies will require appropriate combination of cells, scaffolds and signals (cytokines)
- We can form “cartilage-like” tissue but the overall microstructure and architecture are not normal
  ♦ Standardized, reproducible MR sequences should be utilized
  ♦ Objective evaluation of cartilage following repair
    ♦ Secondary (primary!) end point for FDA trials
  ♦ Quantitative MR evaluation:
    ♦ should ideally assess both PG and collagen
- Registration methodology and careful attention to acquisition parameters (2D, 3D, etc.) and post-processing necessary for multi-institutional trials

References


