Articular cartilage: from Form to Function
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Hollis G. Potter, MD
Chief, Magnetic Resonance Imaging
Director of Research, Dept. of Radiology & Imaging
Hospital for Special Surgery
Professor of Radiology
Weill Medical College of Cornell University

Articular cartilage
♦ Viscoelastic substance with strong imaging and biomechanical anisotropy
♦ Signal properties dependent on:
  ♦ Cellular composition of collagen, proteoglycans and water
  ♦ MR pulse sequence utilized
    ‒ Moderate TE FSE more sensitive to partial thickness lesions
    ‒ Fat suppressed 3D GRE with square voxels more amenable to automatic segmentation and volume quantification methods
♦ Orientation of collagen in different laminae of cartilage

MRI of Articular Cartilage
Imaging Options
♦ Traditional MRI sequences ineffective
♦ 3-D fat suppressed spoiled gradient echo
♦ High resolution moderate TE fast spin echo
♦ Fat suppressed fast spin echo
♦ MR arthrography (direct vs indirect)
♦ Fluid sensitive GRE
  ‒ Driven equilibrium FT (DEFT)
  ‒ Double echo steady state (DESS)
  ‒ Refocused steady state free precession (SSFP)
♦ Ultrashort TE imaging (Bydder)
  ‒ Projection reconstruction spectroscopic imaging

Cartilage Segmentation: 3-D Surface
“Shape view”                              “Thickness view”
(Perpendicular to femur tangent)

Volumetric analysis of articular cartilage
• Cartilage volume: function of both thickness and surface area
  ‑ longitudinal changes affected by alteration in cartilage thickness (elevation or reduction) AND alterations in cartilage surface area (osteophyte formation)
• Cicuttini et al compared tibial cartilage volume and radiographs (JSN/osteophytes) in 252 pts., demonstrating a strong negative linear association between tibial cartilage volume and increasing grade of JSN (Arthritis Rheum 2003; 48:682-688)

• Raynauld et al studied 32 pts with symptomatic knee OA: no statistical correlation between loss of cartilage volume and subjective clinical outcome measures (Arthritis Rheum 2004; 50:476-487)

### HSS Clinical Articular Cartilage Pulse Sequence
- Long TR 3500-5000/ moderate TE 34msec
  - accentuates inherent MTC in FSE: Off-resonance RF pulse saturates the bound pool of water p+ (normally have very short T2); results in ↓ SI from free water p+ after exchange of magnetization
- Adequate FOV to cover anatomy, high matrix (512 x 256-416) imparts superior spatial resolution
- Wider BW (minimize chemical shift, reduce IES)
- Thin slices with no gap

### HSS Clinical Articular Cartilage Pulse Sequence
*JBJS 1998; 80A(9):1276-1286*
- Validated using arthroscopy as the standard (616 surfaces; 88 pts)
- 88 patients (ave. age 38 yrs)
- 3 arthroscopists; 2 independent MR readers
- Sensitivity 87%; specificity 94%; accuracy 92%
  - weighted kappa = 0.93
- MRI within one grade of arthroscopy in 97% (599/616)

### MODIFIED ICRS© CARTILAGE CLASSIFICATION

<table>
<thead>
<tr>
<th>PATHOLOGICAL Change</th>
<th>ARTHROSCOPIC Findings</th>
<th>MRI Findings</th>
<th>MRI Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Articular Cartilage</td>
<td>Grade 0</td>
<td>Normal cartilage with gray scale stratification</td>
<td><img src="image1" alt="Normal Articular Cartilage" /></td>
</tr>
<tr>
<td>Superficial lesions : Chondral softening</td>
<td>Grade 1</td>
<td>Softening to probe</td>
<td><img src="image2" alt="Superficial lesions : Chondral softening" /></td>
</tr>
<tr>
<td>Superficial lesions : Extending down to &lt; 50% of cartilage depth</td>
<td>Grade 2</td>
<td>Fissures / Fibrillation Involving &lt; 50% of cartilage thickness</td>
<td><img src="image3" alt="Superficial lesions : Extending down to &lt; 50% of cartilage depth" /></td>
</tr>
<tr>
<td>Cartilage defects : Extending down to &gt; 50% of cartilage depth down to subchondral bone</td>
<td>Grade 3</td>
<td>Blisters / Fissures / Fibrillation Involving &gt; 50% of cartilage thickness</td>
<td><img src="image4" alt="Cartilage defects : Extending down to &gt; 50% of cartilage depth down to subchondral bone" /></td>
</tr>
<tr>
<td>Penetration of subchondral bone</td>
<td>Grade 4</td>
<td>Exposed subchondral bone</td>
<td><img src="image5" alt="Penetration of subchondral bone" /></td>
</tr>
</tbody>
</table>

**Cartilage Structure: Proteoglycans**
- Chondrocytes comprise <10% of cartilage volume
- Water most abundant component; majority contained within intersitial space created by matrix
- Material properties attributed to extracellular matrix elements (collagen and PG)
- Compressive strength: proteoglycan monomers with neg. charged GAGs (CS or KS) radiate from the protein core
- Monomers bind to HA to form aggregate that resist compression due to hydrophilic structure
- Imaging: assess H+ bound to PG by electrostatic charge (assess fixed charge density)
  - Sodium MRI
  - Gd-DTPA-2 techniques (dGEMRIC)
  - T1 rho imaging

![](image)

**dGEMRIC : delayed Gd-DTPA Enhanced MRI of Cartilage**

T1 following Gd penetration \( \rightarrow \) index of [Gd]cartilage \( \propto \) [GAG]tissue

**dGEMRIC index in clinical studies**

*Williams et al, Amer J Roentgen 182:167, 2004*

<table>
<thead>
<tr>
<th>High</th>
<th>Mid</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 – 600 ms</td>
<td>400 - 500 ms</td>
<td>250 - 400 ms</td>
</tr>
</tbody>
</table>

*Courtesy Deborah Burstein, PhD*

**T1ρ : Assessment of proteoglycan content at 3T**
- Assess low frequency interactions between H+ in macromolecules and free water
- Spin-lattice relaxation in the rotating frame: uses cluster of RF pulses to “lock” magnetization in the transverse plane, followed by a second RF to drive longitudinal recovery
- T1 rho reflects proteoglycan content and correlates to fixed charge density in both trypsinized bovine and clinical osteoarthritis specimens at 4T
- Normalized T1 rho rate (1/T1ρ) was compared to assessment of FCD from Na23 and T1 rho was compared to histology (alcian blue-PAS)
- Percentage change of R1ρ and FCD was highly correlated (R2 >0.85; p<0.001)
- T1 rho values increase as proteoglycan concentration decreases

*Wheaton, Reddy et al. J MRI 2004;20:519-525*
**Cartilage Structure: Collagen**

- Type I collagen fibers provide tensile strength: long ratio of length to thickness
- Intramolecular and intermolecular cross-links provide structural rigidity to the collagen fibrils and prevent slippage or sliding between the collagen molecules

![Collagen Fiber Diagram]

Nimni (1983)

No bound water Water bound helix

*Bella et al. Structure 1995*

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**Cartilage Structure: Collagen**

- Deep radial zone (40-60%): collagen oriented perpendicular to subchondral zone—strong angular dependence: vertical striations evident and short T2 values
- Transitional zone (20-30%): more random collagen orientation—less angular dependence and longer T2s
- Superficial zone (<10%): parallel to surface (beyond resolution of clinical MRI)
- Imaging of collagen orientation and macrostructure
  - Structural anisotropy
  - Quantitative T2 mapping: internuclear dephasing of unbalance dipole interactions: $e^{-\frac{T2^*}{T2}}$

*Xia et al; Osteoarthritis and Cart 2001; 9:393-40*

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**T2 mapping at HSS**

![T2 Mapping Images]

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**Macroscopic Structure at 7T**

![Macroscopic Structure Images]

Note alterations in radial zone striations and T2 values in central versus submeniscal zones

T2 mapping at HSS

- Developed modified multislice multiecho sequence that minimizes the quantitative error generated by stimulated echo formation (J MRI 2003; 17(3):358-364)
  - Suitable for clinically relevant field strengths
- Validated T2 mapping at 1.5T in ovine meniscectomy model and bovine explants using PLM and FTIR-S as standards (AJSM 2006; 34:1464-1477 ; ICRS 2004, 2006)
- Studied in tissue engineered rabbit cartilage (ICRS 2006)
- Currently we have studied over 300 patients following cartilage repair

Angular Dependence of Cartilage: Structural Anisotropy

\[ \frac{1}{T2} = k(3\cos^2 \theta - 1) \]

Intact Collagenase treated

Imaging of Cartilage Structure and Function: Biomechanical testing

- Stress-relaxation test in unconfined geometry
- Static compression (Young’s modulus) followed by dynamic compression (mechanical properties dependent on loading rate)
- Proteoglycans (compressive strength)
  - Gd-DTPA-2 techniques (dGEMRIC)
  - Correlated to static (compressive) strength at 9.4T*
- Collagen fibrils (tensile strength)
  - Quantitative T2 mapping
  - Correlated to dynamic mechanical properties at 1.5T & 9.4T*
    - *Lammentausta et al; JOR 2006; 24:366-374
- Load response to focal indentation as index of stiffness
  - dGEMRIC index of tibial explants at 8.45T correlated to local stiffness when GAG index was normalized to depth of indented tissue but not for the full thickness GAG index
- Dynamic MR elastography to obtain shear stiffness measurement at 1.5T (Lopez et al; JMRI 2007; 25:310-320)
- Age and species related variations affect collagen architecture and assessment of material properties; noted negative linear correlation between equilibrium stiffness and T2 but not dynamic stiffness; dGEMRIC showed no association with mechanical properties at 9.4T (Nissi et al; Osteoarthritis and Cart 2007; 15:1141-1148)
Biomechanical Response to Constant Strain
Relaxation: Apply constant strain, measure stress

Water exudation as matrix relaxes (reorients)
Permeability, K

Water flow ends
Solid matrix resists deformation
Equilibrium Aggregate Modulus, $H_a$

Stress Relaxation

Time $H_a = \text{stress/strain}$

Peter Torzilli, PhD

**Aggregate Modulus vs Histology Grade**
Armstrong & Mow (1982)

Aggregate Modulus vs Histology Grade Score

Osteochondral Matrix Response to
Severe Joint Trauma
Milentijevic D, Aslani K, Potter HG, Torzilli PA

**Stress – Strain Response of Cartilage**

Stress = 60 MPa
Stress Rate = 400 MPa/sec
Shear propagation at high loads (stress = 70-80 MPa)

137 x 137µ x 1.3mm

Safranin-O

1.5T MRI

uCT

Quantitative T2 map

Safranin-O

Polarized Light

Discussion

• No change in maximum compressive strain with high stress magnitudes due to cartilage stiffening
• Superficial cracks occurred due to matrix failure in tension at fissures
• Relative preservation of collagen orientation on PLM and T2 profile despite load
• Subchondral bone compliance appears to protect cartilage during joint trauma

Articular Cartilage Injury following Acute ACL Tear

♦ Spindler et al (AJSM 1993; 21:551-557) evaluated 54 pts with ACL tear and ACLR
  – 46% (25/54) had articular lesion at arthroscopy (LFC>LTP>MFC>MTP)
♦ Johnson et al (AJSM 1998; 26:409-414) evaluated 10 pts with acute ACL tear underwent biopsy of LFC during ACLR
  – Chondrocyte degeneration, loss of PG, osteocyte necrosis and empty lacunae degeneration
♦ Tiderius et al (Arthritis and Rheumatism 2005; 52:120-127) evaluated cartilage glycosaminoglycan loss in the acute ACL injury with delayed post-gadolinium MRI
  – 15 out of 24 patients (63%) had loss of GAG in both medial and lateral femorotibial surfaces
  – Suggests generalized alteration in matrix within the knee cartilage following ACL injury
Cartilage Repair: Methods of Repair

- Articular cartilage has little to no capacity to undergo spontaneous repair
  - avascular; unable to regenerate across a physical gap
- Debridement
- Marrow stimulation (microfracture)
- Osteochondral transfer
  - autologous (mosaicplasty; OATS)
  - allograft (fresh cadaveric tissue)
- Tissue Engineered Cartilage (three requirements)
  - matrix scaffold
    - 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 (growth factors or genes)
- Synthetic acellular techniques (scaffold)
  - polylactide-co-glycolide copolymer and calcium sulfate (porous)

Imaging as a Primary Outcome Measure Morphologic Analysis: Cartilage Repair

- Signal intensity of tissue (ROI analysis)
- Integrity/hypertrophy of periosteal flap (ACI)
- Morphology; presence/absence of displacement (ACI/ OCA)
- Interface with native cartilage
- Volume of repair “fill”
- Appearance/morphology of subchondral bone
- Assess adjacent and opposite articular cartilage
- Presence/absence of inflammatory synovitis

CORR 2004;422: 214-223

MR observation of cartilage repair tissue (MOCART) Marlovits et al; Eur J Radiol 2006; 57:16-23

- MACT assessed in 13 pts at 24 month postop (9 points in grading scale)
  - Degree of fill
  - Integration and structure (homogeneous, clefts)
  - Surface integrity
  - Signal intensity (SI)
  - Subchondral lamina and bone
  - Adhesions and effusion
- Correlated to KOOS and VAS; significant correlation for fill, structure, subchondral bone and SI
- ICC (3 independent readers); $\kappa$ ranged between 0.765-1.00

Microfracture

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

Osteochondral autografts (mosaicplasty)


- Prospective, longitudinal study of cartilage defects treated with hypothermically stored fresh osteochondral allografts using validated clinical outcome instruments and cartilage sensitive MRI
- Allografts remain intact without displacement
  - fissures noted at the graft/host interspace in 16/19 (84%) grafts
  - poor incorporation was noted in 6/19 (32%) grafts, three of which demonstrated an intense bone marrow edema pattern and the remainder of which demonstrated frank subchondral marrow fibrosis (low signal on all sequences)
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

**Quantitative MR Assessment of Articular Cartilage Biochemistry: Clinical Utility**

- **Osteoarthritis**: Breakdown of matrix
  - Swelling of PG, increase cartilage permeability
  - Disruption of collagen with increased mobility of water yielding prolongation of T2 and loss of stratification
    - Assess “disease modifying” abilities of pharmaceutical therapy (viscosupplementation)
    - Optimize timing of meniscal transplantation/realignment/osteotomy

- **Cartilage Repair**
  - Assess components of matrix in repair tissue
  - Assess response of adjacent hyaline cartilage to surgical repair
  - Imaging to serve as a primary outcome variable for the FDA?
  - Obviate the need for second look arthroscopy/biopsy

**Imaging & Cartilage Repair Trials**

- Initial assessment of axial alignment (radiographs)
- Preclinical outcome measures should parallel Phase I and Phase II clinical measures
- Importance of OBJECTIVE outcome measures to assess biology

**Lack of image correlation with functional outcome**

- Spielmann et al, Radiology 1999
  - 15 asymptomatic pts with good to excellent (mean Constant score 86/100) cuff function, s/p open RCR (1.5-5 yr) with MRI
  - 11/30 tendons with partial or FT defects of SST or IST

- Fealy et al, *AJSM* 2006
  - 50 pts 1,3,6 mos s/p RCR with good to excellent function underwent US
  - 48% with defects (50% at 6 weeks, 45% at 3 months, 43% at 6 months)

- Noyes and Barber-Westin, 1995
  - Meniscal transplantation: improvement in pain and function scores were not different between pts with healed or failed transplants

**MRI of Articular Cartilage**

- Standardized, validated sequences available for all joints
- Sequences should not be limited by instrumentation
- Provide noninvasive detection of traumatic injuries
- Monitor progression of cartilage degeneration in OA and disease status in RA
- Provide objective outcome assessment for cartilage repair techniques
- Future development: detect early changes in matrix prior to morphologic alteration
  - noninvasive tissue characterization of repair tissue
  - noninvasive assessment of materials properties
  - optimize timing of meniscal transplantation/PF realignment/osteotomy

**References**


