Advanced Imaging of Arthritis

Andrea S. Doria, MD, PhD, MSc

The Hospital for Sick Children
Toronto, Canada

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## Speaker disclosure

<table>
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<tr>
<th>Conflict</th>
<th>Disclosure - if conflict of interest exists</th>
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<tr>
<td>Research Support</td>
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<td>Advisory Committee</td>
<td>International Prophylaxis Study Group (not for profit); Baxter Steering Committee</td>
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OUTLINE

CLINICAL IMAGING TOOLS

1. Available imaging modalities for early diagnosis - physics characteristics of imaging modalities

2. What is currently available in clinical practice – Data Acquisition and Interpretation

INVESTIGATIONAL IMAGING TOOLS

3. What can potentially be available in clinical practice in the future - Laboratory to clinical translation
Juvenile Idiopathic Arthritis

- Trigger point: antigen (autoimmune)

- Reactive arthritis
  - Vessels grow in an uncontrolled and disorganized manner
  - Vascular pannus
  - Erodes the underlying cartilage

Hemophilic Arthritis

- Trigger point: iron (intraarticular bleed)
Pathologic changes of the knee in JIA:

- Synovial hypertrophy
- Cartilage thinning
- Bone erosions
- Joint effusion
### Functional / Molecular Imaging Targets in Arthritis

<table>
<thead>
<tr>
<th>Target</th>
<th>Process</th>
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<tbody>
<tr>
<td>Flow-mediated vasodilation</td>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>Adhesion molecules</td>
<td>Endothelial activation</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Inflammation</td>
</tr>
<tr>
<td>MMPs, Cathespin</td>
<td>Proteolysis Apoptosis</td>
</tr>
<tr>
<td>Lipid core Fibrous cap</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>αvβ3 integrin</td>
<td></td>
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</tbody>
</table>

**Illustration of physiologic processes in inflammatory arthritis ranging from pre-lesional dysfunction (left) through monocyte recruitment to the development of angiogenesis (right).**

Adapted from Nature Reviews 2004; 3: 914

Question #1 – Arthritis Subtypes

Which are **not** subtypes of Juvenile Idiopathic Arthritis (JIA)?

A. Enthesitis-related arthritis

B. Psoriasis

C. Oligoarthritis

D. Systemic arthritis

E. CRMO
Classification of juvenile idiopathic arthritis (Durban, 1997)

Onset <16 years
Duration: 6 weeks
Subtypes:
1. Systemic arthritis
2. Oligoarthritis
   Persistent
   Extended
3. Polyarthritis (rheumatoid factor negative)
4. Polyarthritis (rheumatoid factor positive)
5. Psoriatic arthritis
6. Enthesitis-related arthritis
7. Other
   Does not meet criteria for any of categories 1-6
   Meets criteria for more than one of categories 1-6
X-Ray and CT

Physics Concept:
Differential absorption of low energy x-rays as they are attenuated during their transmission through the body from source to detector

Advantages:
- High spatial resolution
- CT development with multirow detector systems: improved temporal resolution – potential for measurement of physiologic perfusion rather than only morphologic assessment

Disadvantages:
- Limited soft-tissue contrast sensitivity
- Deleterious x-ray energy absorption
Conventional Imaging
Advanced Imaging - Radiography

Talbot-Lau Interferometer - X-Ray Refraction of 1/10,000 of a Degree

Innovative x-ray device that produces image contrast from phase differences of the x-rays that pass through the target with an ordinary x-ray source. Cartilage does not absorb many x-rays and therefore, it is difficult to photograph. This device produces contrast by detecting x-rays that have bent 1/10,000 degree (Talbot-Lau Interferometry). As a result, tissues that otherwise could not be visualizable by x-rays can be captured.

http://sciencelinks.jp/content/view/1228/365/
Increased number of detector arrays

Nonionic iodinated contrast agents

**Fundamental basis for contrast enhancement in CT**: exchange of small molecules, iodinated contrast material, between the intravascular space and the extravascular interstitial space after intravenous administration.

DOI 10.1007/s00247-005-1575-7

**TECHNICAL INNOVATION**

Stephanie Holowka · Andrea S. Doria

Scan-timed CT angiography in experimental arthritis: selective placement of regions of interest
Physics Concept:

**X-rays:** Differential transmission of external ionizing radiation

**Nuclear Medicine:** Differential radioisotope uptake within a particular organ system using radionuclides of different emitted gamma energy

**PET:** Radionuclides are positron emitters that necessitate coincidence detection = improves contrast to noise through better background suppression
Advantages

1. Ability to spatially localize biologically relevant processes
2. Imaging Merging Technology: PET / CT = high spatial resolution of CT + high specificity of PET radiotracers

Disadvantages

1. Short half-lives of positron-emitting radioisotopes: difficult production and distribution (cyclotron interactions: 18F, 15O, 11C)
2. Possibility of following one molecular species in a given imaging experiment
3. Limited CNR because of excessive absorption (radiation exposure)
4. Tradeoff between spatial resolution (based on collimator designs) and SNR = higher SNR with larger collimator aperture but decreased spatial resolution
Positron Emission Tomography (PET)

Rabbit Model of Blood-Induced Arthritis

PET-MRI Fusion Imaging

- Complementary anatomic and molecular information. Since predicting remission is important but currently limited to score-based methods and timing of treatment affects Prognosis, dual MRI-PET may benefit patients with arthritis by providing a rapid and detailed assessment of disease status and treatment response.

- Challenges: use of radioactive probes and high cost

Fusion of high-resolution 18F-FDG-PET with MRI for a rheumatoid arthritis therapy responder.

Ultrasound

Physics Concept:
Differential reflection of sound waves as they travel through tissue

Molecular imaging application: based on the use of contrast agents ("bubbles")
Conventional Imaging: Advantages of Ultrasound for Evaluation of Arthritic Joints

• Relatively inexpensive imaging modality
• Easy access
• No requirement for sedation for imaging of joints of children under the age of 7 years (as opposed to MRI)
• Color/power Doppler: potential for synovial vasculature visualization without IV contrast administration
• Lack of susceptibility artifacts ("blooming") from extracellular hemosiderin deposition on gradient-echo images
• Ability to differentiate effusion, synovium and hemosiderin
Ultrasound – Capability of Identification of Blood Products?

+ C T1-weighted

PD-weighted

T2-weighted
Differentiation between effusion, synovium and hemosiderin

MRI: sometimes not possible

US: clear differentiation
<table>
<thead>
<tr>
<th>Challenges of Ultrasound for Assessment of Arthritis Joints</th>
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<tbody>
<tr>
<td><strong>DATA ACQUISITION</strong></td>
</tr>
<tr>
<td>- Operator-dependent – Experience is required</td>
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<td></td>
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<tr>
<td><strong>DATA INTERPRETATION</strong></td>
</tr>
<tr>
<td>- Adjustment with MRI scales: suitable for assessment of</td>
</tr>
<tr>
<td>the whole joint (overall assessment), not only the edges</td>
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<tr>
<td>of the joints</td>
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<tr>
<td>- Quantification of diagnostic test sensitivity loss and</td>
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<tr>
<td>correlation with clinical significance</td>
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<tr>
<td>- Need for normative data for comparison of physiologic</td>
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<tr>
<td>and pathologic cartilage thinning (true for both US and</td>
</tr>
<tr>
<td>MRI)</td>
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</tbody>
</table>
Limited Field-of-View of Ultrasound Imaging

L2 Ant Sag Med
Cor T2

US “sees” only the external aspect of the articular surface
Limitations of Ultrasound Compared with MRI

**Cartilage**

Central portion cannot be visualized on US - most of the osteochondral changes are seen at the periphery of the joint

Posterior aspect of patella cannot be visualized on US

Challenges on positioning of transducer (angle of ultrasound beam)
Sonography for assessment of haemophilic arthropathy in children: a systematic protocol

K. ZUKOTYNSKI,§ J. JARRIN,* P. S. BABYN,*§ M. CARCAO,†‡ J. PAZMINO-CANIZARES,‡
A. M. STAIN† and A. S. DORIA*§
*Departments of Diagnostic Imaging and †Pediatrics, Division of Hematology/Oncology; ‡Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada and §Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada

Refinement of a sonographic protocol for assessment of haemophilic arthropathy

S. KESHAVA,* S. GIBIKOTE,* A. MOHANTA† and A. S. DORIA†
*Department of Radiology, Christian Medical College Hospital, Vellore, India and †Department of Diagnostic Imaging, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada
Transducer position in the sagittal plane for ultrasound scanning of knees and ankles.

Keshava et al. Haemophilia 2009
CARTILAGE LOSS

L1 Ant Sag Lat

L1 Ant Ax Med

Sag PD
Advances

Real-time 3D imaging

Ultrasound biomicroscopy

Tissue characterization with specifically designed contrast agents
Which is **not** an advantage of 3DUS over conventional 2DUS imaging for assessment of arthritis?

A. Improved reliability and reproducibility in serial measurements

B. Electronically controlled transducers: less motion artifact with the use of mechanical arms

C. Possibility of compression of images during scanning
Advanced Imaging: Advantages of 3DUS for Evaluation of Arthritic Joints

- Images in different viewing planes can be reconstructed using 3D data acquired, including the coronal plane which is not always possible in 2D

- Improved reliability and reproducibility in serial measurements

- Superior visualization of the synovial space (compared to 2DUS) including subtle changes in the microvasculature and morphology of the synovial membrane and articular cartilage

- Electronically controlled transducers: 2DUS transducers are held and controlled manually. 2DUS imaging requires that users mentally integrate 2D images to form an impression of 3D structures
Advanced Imaging: Disadvantages of 3DUS

- Mismatches between the motorized linear scanning mechanism and the irregular contour of the knee with loss of contact during scanning
- Reconstruction into a single combined 3D image of the knee requires co-registration of images: time consuming
- More cumbersome process: involves adding a mechanical motor to the transducer and may be more difficult for the user to manipulate.
- On 2DUS, the operator can compress the area being imaged which is difficult to be implemented at 3DUS
- Using the motorized linear scanning mechanism, color Doppler suffers from motion-related artifact, indistinguishable from true signal

Possible solutions:
Use of a different position sensing mechanism such as a magnetic-track probe or a curved scanning mechanism.
3DUS Data Acquisition Techniques

- **Free-hand scanning without position sensing** – 3D images are reconstructed on the assumption that the operator is moving the transducer in a smooth, steady motion while capturing 2D images at regular intervals in a linear or angular fashion - highly user dependent.
- **Free-hand scanning with position sensing** – Uses a transducer with articulated arms and magnetic field sensors to track the position and orientation of the US probe.
- **Two-dimensional array scanning for dynamic three-dimensional US** – Uses a stationary 2D transducer array to generate real-time 3D images.
- **Mechanical scanning** – Uses a motorized mechanism to translate, tilt, or rotate a conventional transducer to acquire a sequential series of 2DUS images.
Setup for 3DUS

Hardware and software:

a. 3D hardware coupled with the conventional ultrasound transducer.

b. Enlarged view of motorized mechanism attached to a conventional 2DUS transducer used to translate the transducer and capture a linear series of 2DUS images

c. 3DUS software (Wing) that enables real-time images to be visualized in 3D during scanning
Sagittal 3DUS (a) and 2DUS (b) images of the suprapatellar pouch with joint effusion, and axial 3DUS (c) and 2DUS (d) images of the distal femur in a patient with JIA.

3D reconstructions allow users to have a better appreciation for the 3D anatomy (i.e., cartilage volume).

Images can be reproduced in any plane – as in a virtual patient.
**3DUS-MR Fusion Imaging**

- **Definition**: superposition of US and MRI images
- **Potential advantages** of 3DUS-MR fusion imaging:
  - Allows users to merge real-time US images with retrospective MR images, which can improve US operator confidence, as well as anatomical and functional correlations
  - Provides MRI reference points as anatomic landmarks in serial US examinations, which may improve reproducibility in disease follow-up and therapy monitoring
- **Disadvantages**: extra cost and time associated with its use

Sagittal T1-weighted MR image of the knee with a joint effusion with ROI (green) corresponding to a sagittal 3DUS image at the level of L0 central.
Ultrasound Biomicroscopy

CARTILAGE

Lesion not seen macroscopically

Doria et al. Pediatr Radiol 2004
Ultrasound Biomicroscopy
CARTILAGE

Normal
11 mm

Lesion seen macroscopically

Lesion not seen macroscopically

Doria et al. Pediatr Radiol 2004
Contrast-Enhanced Ultrasound

Principles for Use in Molecular Imaging:

1. If the wavelength of the transducer is matched to the properties of a given contrast agent bubble, a specific signature can be measured.

2. The US probes receive signals based on the collapse of the bubble during US scanning.
SOFT TISSUES

Contrast-Enhanced Ultrasound - Humans

Doria et al. Pediatr Radiol 2001; 31: 524-531
Microbubble destruction-reperfusion technique:
• measures the regional blood flow and vascular volume

\[ R(T) = a (1 - e^{-bt}) \]

• (b) a mean velocity
• Initial slope a flow rate
• Asymptote (A) a vascular volume

Contrast-Enhanced Ultrasound
Rabbit Model of Inflammatory Arthritis (Antigen: Albumin)

Flow rate

Mean velocity

Day 1 of arthritis

Day 14 of arthritis

*Doria et al. Pediatr Radiol 2006; 36: 1242–1251*
Optical Imaging

Physics Concept:
Light microscopy is the primary tool for biologic imaging at the **cellular level**

**Advantages:**
- High temporal resolution
- Good SNR

**Disadvantages:**
- Molecular level
- Small depth of tissue penetration, which is limited by absorption and scattering of light
Optical Imaging

BIOLUMINESCENCE

**Principle**: occurs when the energy is supplied by a biochemical reaction
Optical Imaging

PHOTOACOUSTIC IMAGING (PAI)

Principle: a short-pulsed laser is used to illuminate the tissue sample and generate photoacoustic waves due to the transient thermoelastic expansion in the tissue. PAI is highly sensitive to molecular conformation of biological tissues and can aid in describing tissue functional hemodynamic changes such as angiogenesis and hypoxia in pathologic synovium, providing imaging at cellular and molecular levels.

Chamberland D et al. Integr Biol (Camb) 2010; 2:496-509
**MRI**

**Physics Concept:**

Interrogation of tissue water protons through the differential population of proton spins

**Limitations:**

Resolution and SNR are dependent on gradient strengths, radiofrequency RF coils and main magnetic field strength

**Use of MRI in functional imaging:**

Indirect detection mode by watching the influence on tissue relaxations resulting from sequence parameters designed to capture signal at specific points in the relaxation curve (e.g. BOLD) or with the use of contrast agents (e.g. gadolinium, iron oxide)
Which is an MRI technique that estimates of the physiologic properties of the synovial microvessels in JIA, including blood/plasma volume, and transendothelial permeability of the contrast agent?

A. MR Spectroscopy

B. Dynamic MRI (positive contrast agent: gadolinium)

C. Blood oxygen level dependent (BOLD)

D. MRI (negative contrast agent: ultrasmall paramagnetic iron oxide [USPIO])

E. Diffusion-weighted imaging
Conventional MRI

Synovitis

- T1/PD
- Gadolinium

Sag T1

Ax T1 fat sat
Conventional MRI

Osteochondral Abnormalities

- Cartilage loss
- Erosions
- Subchondral cysts
Today's Imaging

Data Acquisition
1.5 vs 3 Tesla MRI Scanners

3D SPGR  FS SSFP  Dixon

High Resolution Coils

Finger: 47 mm microscopy coil. FFE, TE 10 ms.
75% reduction in scanning time using parallel imaging rather than conventional imaging.

The use of parallel imaging for MRI assessment of knees in children and adolescents

Andrea S. Doria • Gulraiz A. Chaudry • Cristina Nasui • Tammy Rayner • Chenghua Wang • Rahim Moineddin • Paul S. Babyn • Larry M. White • Marshall S. Sussman
WHOLE BODY MRI

Protocol for ERA:

Cor STIR Multistation (scan time: 28 min)
Sag STIR Spine
Ax obl STIR SI joints
Cor obl STIR SI joints
Sag STIR Knees
Sag STIR Ankles (scan time: 30 min)

Scan time: 58 min

Body coil
Results of this study: The semi-quantitative method is valid for assessment of pathologic cartilage status in cross-sectional studies of blood-induced arthropathy in ankles, however the quantitative method is suboptimal or less powerful for this purpose.

The cartilage thickness (ThCtAB) in the talar trochlea measured 1.22 units and in the distal tibia, 1.05 units.

<table>
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<tr>
<th>Tissue</th>
<th>Measurement</th>
<th>MRI sequence / technique</th>
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<tbody>
<tr>
<td>Synovium</td>
<td>Fluid</td>
<td>T2-weighted fast spin-echo MRI</td>
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<td></td>
<td>Rate of transfer of contrast between plasma and extravascular extracellular space</td>
<td>Dynamic contrast-enhanced MRI</td>
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<td></td>
<td>Restricted water motion (inflammation proxy)</td>
<td>Diffusion tensor imaging</td>
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<tr>
<td>Cartilage</td>
<td>Cartilage hydration and collagen orientation</td>
<td>T2-mapping MRI</td>
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<td></td>
<td>Glycosaminoglycan content</td>
<td>Delayed gadolinium enhanced MRI</td>
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<td></td>
<td>Proteoglycan depletion</td>
<td>23Na MRI</td>
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<tr>
<td></td>
<td>Proteoglycan content</td>
<td>T1 rho MRI</td>
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<tr>
<td>Bone</td>
<td>Erosions</td>
<td>T1-weighted MRI</td>
</tr>
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<td></td>
<td>Bone marrow edema</td>
<td>T2-weighted fast spin-echo or short tau inversion recovery (STIR) MRI</td>
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</table>
Changes in Blood Oxygenation level cause changes in MR Decay of T2*
Inflammation → Metabolic demand → Oxygenation → ANGIOGENESIS

Vascular system of the knee

Artery → Synovial cell → Vein

**Synovial cell**

**O2 consumption**

**Timepoints**

<table>
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<tr>
<th>BOLD signal on</th>
<th>BOLD signal off</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>28</td>
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</table>

**Acute Arthritis** (day 1)

BOLD signal intensity decreases / increases reflecting decrease in venous pO2 (increased oxygen extraction) or synovial hyperemia

**Chronic Arthritis** (day 28)

BOLD signal intensity returns to baseline values

**Hypothesis**

Negative correlation: BOLD = synovial hyperemia

**Alternative**

Positive correlation: BOLD = oxygen extraction

**BOLD MRI - Rationale**

Arthritic knees

pO2 vein
**BOLD MRI** is feasible to depict synovial changes during progression of experimental arthritis. We did not define the biological basis for the BOLD MRI changes noted over time since histologic assessment did not explain the physiologic events of the experiment. Required further validation of the technique.
Region-of-Interest–based Analysis of Clustered BOLD MRI Data in Experimental Arthritis

Andrea S. Doria, MD, MSc, PhD, Paul Dick, MD, MSc

Reliability and Convergent Validity of Different BOLD MRI Frameworks for Data Acquisition in Experimental Arthritis

Andrea S. Doria, MD, MSc, PhD, Chenghua Wang, Anguo Zhong, Tammy Rayner, Jaques Belik, Rahim Moineddin, Adrian Crawley

Acad Radiol 2005; 12: 841-852

Acad Radiol 2011; 18: 615-626
BOLD imaging correlated moderately (r = .54, P < .0001) with knee diameters, and weakly (r = .35, P = .01) with laboratory indices (high threshold for analysis).
Results of this study show that numerically BOLD MRI values were greater in knees with active inflammation than in contralateral unaffected knees, and interval pre- and post-injection changes were greater in the arthritic group than in the group of contralateral joints.

Translation to Humans (JIA Patients) at 3.0 Tesla

JIA patient – Bilateral knee involvement, right worse

CO2 Challenge

Percentage (%) BOLD signal change
a. Pathologic: median [SD], 1.27 [0.84])
b. Asymptomatic: median [SD], -0.31 [0.08]
c. Median [SD], 0.12 [0.32])
Expected BOLD signal in arthritic, asymptomatic contralateral and healthy joints and oxyhemoglobin/deoxyhemoglobin ratios
DCE MRI of the inflamed synovium: provides estimates of the physiologic properties of the synovial microvessels, including blood/plasma volume, and transendothelial permeability of the contrast agent.

Gd-DTPA: Microvascular agent

Parameters:
- Time-to-peak (TTP)
- Signal enhancement
- Peak enhancement

Results in this study:
In arthritic knees increased capillary permeability is expected to take place in early disease as compared with baseline, mid-term (day 14 of arthritis) and late disease (day 28 of arthritis) measurements.

Doria et al. AJR 2006; 186: 1165-1171
Dynamic Contrast-Enhanced MRI: In vivo capillary permeability and signal slope have distinctive dynamic MRI properties. The accuracy of MRI parameters for diagnostic evaluation of experimental arthritis differs according to the stage of disease.

Difference of AUCs: time-to-peak (TTP) and other parameters on day 1, $P = 0.0002$ and signal slope ($dS/dt$), capillary permeability ($kPSr$) and other parameters on day 14, $P = 0.001$
Ultrasmall Superparamagnetic Iron-Oxide Contrast Agents (USPIO) MRI

SYNOVIUM

A

Activated T cell

B cell

Rheumatoid factor

Unknown antigen

Macrophage

Superparamagnetic iron oxide (SPIO) particles

Macrophage engulfing SPIOs

Femur

Tibia

2 hour post-RA induction

4 hour post

Macrophage trafficking, MR Imaging

Biswal S. Arthritis in Color. Saunders, 2009
Ultrasmall Superparamagnetic Iron-Oxide Contrast Agents (USPIO) MRI

Rabbit Model of Blood-Induced Arthritis

Pre-contrast

Post-contrast (48 hr after injection)

NEGATIVE contrast agent

Amirabadi, Doria et al. World Federation of Hemophilia, Buenos Aires, 2010
Sensitive to cartilage proteoglycan content

Due to negatively charged glycosaminoglycans (GAG) sidechains, proteoglycans attract cations and water into the tissue, causing a swelling pressure.

T1 relaxation time in presence of the contrast agent is linearly related to the GAG content.
T1 rho MRI
CARTILAGE

Able to detect early intracartilaginous degeneration quantitatively and also qualitatively by color mapping demonstrating a higher sensitivity than standard T2-weighted sequences. The results of this technique highly correlate with reduced proteoglycan content and disrupted collagen architecture as measured by biochemistry and histology.


Area of inhomogeneity
T2 Mapping MRI

CARTILAGE

T2 measurements may characterize the structural integrity of the cartilaginous tissue and quantitatively assess the degree of cartilaginous degeneration (proteoglycans).

Spatial variation of T2 correlates with the 3D arrangement of the collagen fibrils.

Potential: detection of proteoglycans changes prior to anatomic damage.

Dardzinski et al. Radiology 2002
HEMOPHILIC ARTHROPATHY

Overall decrease in average T2 values in arthritic knees over time regardless of the use or not of USPIO contrast agent (P<0.0001)

Amirabadi, Doria et al. ISMRM 2009
T2 Mapping of Cartilage – Picrosirius Staining

Baseline - Medial

Week 10 - Medial
Diffusion-Weighted MRI

CARTILAGE / BONE

- Demonstrates the normal translational movement (Brownian motion) of water molecules that occurs in all tissues.

- Alteration of normal diffusion can occur in pathological events with a loss of tissue integrity. This technique is promising for evaluating ischemic tissues, and functional changes associated with osteoporosis.

Diffusion Tensor Imaging (DTI)

CARTILAGE

- Characterizes the in vivo 3D arrangements of collagen fibres

- Allows determination of the directionality as well as the magnitude, form, trend and integrity of a particular anatomic region [Govoni et al 2004].

The highly ordered structure of the collagen matrix is induces anisotropy in the diffusivity of water, so that measuring the anisotropy of diffusion could give direct information on the integrity of the collagen matrix. Also, DTI may be sensitive to the proteoglycan (PG) content through mean diffusivity. Therefore, it is a promising technique for the diagnostic workup of articular cartilage, especially since it may be sensitive to both PG content and collagen fiber architecture.

MicroMRI

- Acquires images at a resolution sufficient to visualize individual bony trabeculae and to obtain quantitative information in the form of structural parameters similar to those of histomorphometry

The in-plane image resolution with this technique is approximately 156 micrometers which is similar to the dimensions of the bony trabeculae (78-200 micrometers)

Wehrli et al. Radiology 1998
Physics Concept:

Detects protons on a molecule which have a unique signature that can be discerned in an MR spectroscopy experiment

Disadvantages:

Low SNR
MRI Spectroscopy - METABONOMICS

**Principle**: 1H NMR spectroscopic analysis of biofluids enables the generation of spectral profiles of a wide range of **low molecular weight metabolites** that reflect the metabolic status of an organism.

Perturbation of the homeostatic system of an organism by drug-induced toxicity or disease initiates a metabolic change detectable in the spectral profile.

**The Problem**: With advancement of MRS technology: visual analysis was not the optimal way to interpret biofluid spectra (too complex).

**Metabonomics**: Systems approach to investigating the metabolic consequences of (patho)physiological or genetic modification in a multivariate and dynamic manner. Enables interpreting large databases of 1H NMR urine and plasma spectra in various states of health and disease.

*Holmes & Antti. Analyst 2002; 127: 1549-1557*
Stackplot of 600 MHz 1H NMR spectra of urine obtained from rats treated with tissuespecific toxins

Strategy of metabonomic ‘expert system’ for toxicity screening

Holmes & Antti. Analyst 2002; 127: 1549-1557
Hyperpolarized MRI

Purpose: Polarization of metabolically active substrates such as **pyruvate** permits in vivo metabolic imaging of the injected agent and downstream metabolic products. The metabolic products can be differentiated from the substrate on the basis of their chemical shifts. Pyruvate levels are elevated in joints affected by osteoarthritis, and the amount of lactic acid, a metabolic product of pyruvate, is elevated in the synovial fluid of patients with rheumatoid arthritis.

**Advantages:**

- increased sensitivity in the 13C MRS experiment by 10,000-fold or more
- detection of 13C-labeled substrates in vivo plus imaging of their tissue distribution
- Absence of background signal from nonpolarized material


MRI

Clinically available

Hardware
- High strength field MRI: 1.5 and 3 Tesla scanners
- High resolution coils

Software
- Parallel imaging: faster scanning
- 3D Reconstruction

Investigational

Bone: osteoporosis - MicroMRI

Synovium: DCE MRI, USPIO, BOLD

Cartilage: T2 mapping
The Future

**Integrative Systems Approach** to:

- Disease Diagnosis
- Treatment
- Monitoring
Intuition becomes increasingly valuable in the new information society precisely because there is so much data.

John Naisbitt 1929-