Liver Fat and Iron Quantification

40th Annual Meeting of the SCBT/MR
Nashville, TN
September 11, 2017
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Disclosures

• University of Wisconsin-Madison receives research support from GE Healthcare, and Bracco Diagnostics
• Founder – Calimetrix, LLC
• Shareholder – Elucent Medical, Reveal Pharmaceuticals
• Consulting - Parexel International
Case: 61yo obese female

- Obese, type II diabetes
- No known liver disease, No EtOH
- Presents with cryptogenic cirrhosis
- Develops HCC 1 year after presentation
- Necessitated liver transplant

**Presumed Etiology:** Non-Alcoholic Fatty Liver Disease
Non-Alcoholic Fatty Liver Disease (NAFLD)

• First described by Ludwig et al (Mayo Clin Proc 1980)
• Most common cause of chronic liver disease
  – 30% of people in the USA (100 million) have fatty liver disease
    (Harrison et al, ClinLivDis 2004)
  – 10% of all children have fatty liver disease
    (Schwimmer et al, Semin Liver Dis 2007)
• Fatty liver can progress to injury and scarring, leading to
  – Cirrhosis
  – Liver failure
  – Hepatocellular carcinoma (HCC)
• Fatty Liver Disease: a feature of the “Metabolic Syndrome”
  – Obesity, Diabetes (type II)
  – Increasing cause of cancer, cardiovascular disease, Diabetes type II
  – Underlying etiology: Insulin Resistance
Classes of Fat Quantification Methods

1. With/without fat suppression
   - eg. compare T2 without and out fat saturation

2. “Magnitude MRI” (M-MRI)
   - Two or more magnitude images acquired in/opposed phase

3. “Complex MRI” (C-MRI)
   - Chemical shift based water-fat separation from complex source images
Imaging Methods for Quantifying NAFLD

Water

Fat

Measured signal

add…
Chemical Shift Based Fat-Water Separation

Fat-Fraction independent of coil sensitivity
Proton Density

One “voxel” of water

One “voxel” of triglycerides

Is the proton density the same?
**Definition:** Proton Density Fat-Fraction

- Ratio of …
  - Number of protons of mobile triglycerides and
  - Number of protons of mobile water + mobile triglycerides

\[
\frac{F}{W + F}
\]

- Protons in bound lipids are not MR visible
  - Cholesterol, sphingolipids, phospholipids, etc

- **Fundamental property of tissue**

Reeder et al JMRI 2012
Quantitative Biomarkers of Steatosis

*Confounding Sources of Bias*

- Quantitative MRI biomarker for fat requires consideration of …
  - $T_1$ bias
  - $T_2^*$ decay
  - Multiple fat peaks
  - Temperature
  - Noise bias
  - Eddy Currents
  - Concomitant gradients

Magnetic Resonance Imaging - Conventional (MRI-C) has more Potential Sources of Bias, but has Larger Dynamic Range: 0-100% Fat Fraction
Genetic Hemochromatosis?

Severe Steatosis?

Opposed Phase?

For IOP imaging, fat and iron have opposite effects!

$TE = 4.8\, ms$  $TE = 2.4\, ms$
Simultaneous Estimation: $R_2^*$, Water, Fat

- Combined $T_2^*$ into signal model
- Yu et al JMRI 2007 (MRI-C)
- Bydder et al MRI 2008 (MRI-M)
- O’Regan 2009 Radiology (MRI-C)

Yu et al, MRM 2007
Sources of Bias: *Multiple Peaks of Fat*

- Many metabolites have more than one spectral peak
  - Fat has multiple spectral peaks, several near water
  - Leads to incomplete separation of water and fat
  - Source of “gray” fat on many fat suppression methods
Confounder-Corrected MRI: MRI-C vs MRS

No MP
No R2*

With MP
No R2*

No MP
With R2*

With MP
With R2*

Meisamy et al
Radiology 2011
Confounder-Corrected MRI: MRI-C vs MRS

\[ y = 0.9853x + 0.5933 \]
\[ R^2 = 0.97639 \]

Fananapazir et al ISMRM 2013
Confounder-Corrected MRI: MRI-C vs MRS

Data courtesy Claude Sirlin, MD

- Three sites
- 7 magnets
- 1.5T, 3T
- Two vendors

Reproducible!
# Treatment Monitoring:

**Weight Loss from Bariatric Surgery**

<table>
<thead>
<tr>
<th>Day</th>
<th>Weight</th>
<th>Day</th>
<th>Weight</th>
<th>Day</th>
<th>Weight</th>
<th>Day</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>-21</td>
<td>160kg</td>
<td>-13</td>
<td>158kg</td>
<td>-1</td>
<td>154kg</td>
<td>+90</td>
<td>130kg</td>
</tr>
</tbody>
</table>

![Image showing MRI scans with percentage loss]
Example of Quantitative Threshold:

**Hepatic Steatosis**

- Metabolic Syndrome
  - PDFF > 3.0% threshold
  - AUC = 0.81
  - Sensitivity = 80%
  - Specificity = 81%

Rehm et al Eur Radiology 2015
Quantitative Biomarkers of Fat

- FDA approved
  - GE Healthcare, Philips, Siemens*

- Majority of the technical development complete
  - Low PDFF quantification major remaining question

- Remaining unanswered questions
  - Thresholds for normal vs abnormal are unknown
  - Precise role in clinical care pathways
  - Complementary role with biopsy and other non-invasive biomarkers

*510k submitted, approval pending
Case: 51 yo M with Genetic Hemochromatosis

Cirrhosis, TIPSS
High risk for HCC
On transplant list
Iron overload

• Two main causes:
  – *Hemochromatosis* (hereditary)
    Excess intestinal absorption
  – *Hemosiderosis* (transfusional)
    Repeated blood transfusions for anemias, SCD, MDS,…

• Excess body iron is highly toxic, can lead to
  – Liver damage (cirrhosis, liver failure, cancer)
  – Pancreatic dysfunction (diabetes, exocrine insufficiency)
  – Heart failure (cardiomyopathy, sudden death)
Treatment for Iron Overload

- **Phlebotomy** (*hereditary hemochromatosis*)
  - Regular extractions of ~500 ml blood
  - Requires monitoring of iron levels to adjust frequency of phlebotomy

- **Chelation therapy** (*transfusional hemosiderosis*)
  - Chelators bind to excess iron and facilitate removal from the body
  - Expensive (> $40,000/year) and carries its own toxicities
  - Monitoring of iron levels is critical
    - *Maintain low body iron*
    - *Minimize treatment side effects*
MRI Quantification of Iron

Two main approaches currently available

- $R_2$ mapping ($R_2 = 1/T2$)
- $R_2^*$ mapping ($R_2^* = 1/T2^*$)

$R2^*$-weighted images (chelation therapy)

Baseline 4 months 8 months

C. Sirlin, S. Reeder, MRICNA 2010
Gradient Echo vs Spin-Echo

Refocusing Pulse
- R2 = 1/T2
- R2 mapping also sensitive to iron
- R2 less sensitive to iron than R2*
- Older technique
- Longer scan time

“Gradient Echo”
(e^{-TE/T2*})

“Spin Echo”
(e^{-TE/T2})
Biomarkers for Iron

$R_2$ mapping

http://www.ferriscan.com/
MR Biomarkers for Iron: $R2^*$ mapping

- $R2^*$ is very sensitive to the presence of iron
- Fast – whole liver coverage in single breath-hold

Acquired images

- No iron overload: slow signal decay
- Iron overload: fast signal decay

R2* maps

- 36
- 17
- 532
- 334
MR Biomarkers for Iron: $R2^*$ mapping

Treatment monitoring for iron overload

**Before therapy**

- 21 year old cancer survivor undergoing chelation therapy
  - **R2* = 315 s⁻¹**
  - 3 months

- 5 year old boy with Blackfan-Diamond anemia, undergoing chelation therapy
  - 65 s⁻¹
  - 105 s⁻¹
  - 49 s⁻¹
  - **R2* = 185 s⁻¹**
  - 1 year

- 65 yo woman with hemochromatosis undergoing phlebotomy
  - **R2* = 185 s⁻¹**
  - 400 s⁻¹
  - 120 s⁻¹
  - 0 s⁻¹
  - 450 s⁻¹
  - 1 year

**After therapy**

- **R2* = 270 s⁻¹**

- **R2* = 96 s⁻¹**
R2* Confounding Factors

• Fat
  – 20-30% of US population has liver fat
  – Related to type II diabetes and obesity
  – Commonly coexists with iron overload

• Magnetic susceptibility
  – Air-tissue interfaces
  – Important for heart and liver

• Noise floor effects

• (Magnetic Field Strength)
**Case:** 31 yo man with family Hx of hemochromatosis, elevated ferritin. MRI ordered to r/o iron overload

**Conventional IOP Imaging**
Signal dropout on opposed phase imaging *consistent with steatosis only*

**Complex MRI**
- **Severe steatosis:** PDFF = 28% (normal < 5-6%)
- **Mild iron overload:** $R_2^*=90s^{-1}$ (normal < 50-60s$^{-1}$)

**Diagnosis:** NAFLD and hemochromatosis
(Iron overload missed on IOP imaging)
Case: 31 yo man with family Hx of hemochromatosis, elevated ferritin. MRI ordered to r/o iron overload

H&E (4x)  Perl’s Blue (10x)
Magnetic Field Strength

Signal decay depends on field strength
- Must calibrate for each field strength
- 10-20% of market uses 3T
- eg. 7 of 17 scanners at UW are 3T
Calibration: $R2^*$ vs $HIC$

1.5T

$y = 26.57x + 25.08$

$R^2 = 0.90$

3.0T

$y = 53.59x + 34.17$

$R^2 = 0.91$
R2* maps vs HIC maps

1.5T

R2* maps

HIC maps

3.0T

0 s⁻¹

400 s⁻¹

0 mg/g

7 mg/g

179 s⁻¹

349 s⁻¹

5.79 mg/g

5.87 mg/g
Rapid Fat-Iron Quantification Protocol

Localizers (15s) Quantitative CSE-MRI (15s) Axial T2-SSFSE (20s)

Proton Density Fat-Fraction 100% R2* 110s⁻¹

45% 0% 40s⁻¹ 0s⁻¹

Diagnosis: NAFLD

Total scan time < 1 minute, Total table time < 5 min
Thank you!

- Diego Hernando, PhD
- Samir Sharma, PhD
- Ryan Mattison, MD
- Rachel Cook, MD
- Jen Kuehn, MD
- Claude Sirlin, MD

Grant Support
- WARF Accelerator
- NIH: R01 DK083380
  R01 DK088925
  R01 DK100651
  K24 DK102595