Liver Fat and Iron Quantification

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Scott B. Reeder, MD, PhD

Department of Radiology
University of Wisconsin
Madison, WI
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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)

- 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
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

MRI-C has more Potential Sources of Bias, but has Larger Dynamic Range: 0-100% Fat Fraction
Genetic Hemochromatosis

For IOP imaging, fat and iron have opposite effects!
Simultaneous Estimation: R2*, 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
Confounding-Corrected MRI: MRI-C vs MRS

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

MRI-M at 1.5T

$\text{r}^2=0.97$

slope = 0.98 +/- 0.02, p=0.18

intercept = 1.0% +/- 0.2%, p=1x10^{-5}

Siemens 1.5T

MRI-M at 3.0T

$r^2=0.98$

slope = 0.98 +/- 0.01, p=0.08

intercept = -0.09% +/- 0.1%, p=0.5

GE 3.0T

Reproducible!

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

Data courtesy Claude Sirlin, MD
Treatment Monitoring:

Weight Loss from Bariatric Surgery

Day -21
160kg

Day -13
158kg

Day -1
154kg

Day +90
130kg

15%
14%
12%
3.5%
Example of Quantitative Threshold:  

**Hepatic Steatosis**

- $r^2 = 0.97$, $p < 0.001$
- Slope = 0.983
- Intercept = 0.795

- **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 ($R_2 = 1/T_2$)
- $R_2^*$ mapping ($R_2^* = 1/T_2^*$)

$R_2^*$-weighted images (chelation therapy)

Baseline 4 months 8 months

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

RF

Refocusing Pulse

- $R_2 = 1/T_2$
- $R_2$ mapping also sensitive to iron
- $R_2$ less sensitive to iron than $R_2^*$
- Older technique
- Longer scan time

"Gradient Echo"
($e^{-TE/T_2}$)

"Spin Echo"
($e^{-TE/T_2^*}$)
Biomarkers for Iron

$R_2$ mapping

http://www.ferriscan.com/

St. Pierre et al Blood, 2005
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

21 year old cancer survivor undergoing chelation therapy

5 year old boy with Blackfan-Diamond anemia, undergoing chelation therapy

65 yo woman with hemochromatosis undergoing phlebotomy

Before therapy

After therapy

R2* = 315 s⁻¹
R2* = 270 s⁻¹

R2* = 185 s⁻¹
R2* = 96 s⁻¹

3 months
1 year
120 s⁻¹
450 s⁻¹

0 s⁻¹
400 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
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
- 179 s⁻¹

HIC maps
- 5.79 mg/g

3.0T

R2* maps
- 349 s⁻¹

HIC maps
- 5.87 mg/g
Rapid Fat-Iron Quantification Protocol

**Localizers (15s)**

**Quantitative CSE-MRI (15s)**

- Proton Density Fat-Fraction 100%
- 45%
- 40s⁻¹
- 0%
- 110s⁻¹

**Axial T2-SSFSE (20s)**

**Diagnosis:** NAFLD

Total scan time < 1 minute, Total table time < 5 min
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