Quantitative diffuse liver biomarkers

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I am Founder & CEO of the spin-off company QUIBIM which provides a service of Imaging Biomarkers.
Learning objectives

• To learn how to model simultaneously fat and iron within a same signal

• To understand the basics of main quantification methods for diffuse liver disorders

• To learn models for fibrosis and inflammation characterization
• Introduction

• Quantifying fat and iron deposits

• Quantifying fibrosis and inflammation

• Conclusions
Liver biopsy is one of the main diagnostic techniques for the detection of several hepatic disorders such as steatosis, iron deposits, inflammation and fibrosis, commonly associated with diffuse liver diseases.

This technique is an invasive and expensive procedure that can lead to complications and which, due to the small tissue sample, might provide biased results.
The measurement of liver fat, iron and macromolecules environment based on MR imaging allows to reveal tissue abnormalities before any symptoms appear, providing a reliable method to monitor the effects of a treatment.

The most relevant are the proton density fat fraction (PDFF), the iron related $R_2^*$, the diffusion alterations, the $T_1$ and the $T_2$. 
**Introduction**

<table>
<thead>
<tr>
<th>Tissue Deposit</th>
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<tbody>
<tr>
<td>Fat</td>
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<tr>
<td>Iron</td>
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Fibrosis - Collagen and Inflammation
# Introduction

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<td>T1, ADC, VIM parameters, Stiffness, Young's modulus, T2</td>
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- **Fat**: PDFF
- **Iron**: R2*
- **Fibrosis, Collagen and Inflammation**: T1, ADC, VIM parameters, Stiffness, Young’s modulus, T2
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<td>Multi-Echo Chemical Shift (MECSE)</td>
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<td>Multi-flip angle or IR Look-Locker</td>
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<td>Fibrosis - Collagen and Inflammation</td>
<td>T1</td>
<td>Diffusion with multiple b-values</td>
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<td>Stiffness - Young’s modulus</td>
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<td>Elastography</td>
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<tr>
<td>T2</td>
<td></td>
<td>Multi-echo FSE</td>
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**Introduction**

- **Tissue deposit**
  - Fat
  - PDFF
- **Imaging Biomarker**
  - R2*
- **MR sequence**
  - Multi-Echo Chemical Shift (MECSE)
  - Multi-flip angle or IR Look-Locker
  - Diffusion with multiple b-values
  - Elastography
  - Multi-echo FSE
Quantifying fat and iron deposits
Fat and iron are the most common parenchymal deposits in diffuse liver diseases.

In patients with NAFLD and non-alcoholic steatohepatitis, hepatic iron overload is frequently present and associated with disease severity and fibrosis development.

Coexisting steatosis in patients with iron overload acts as an important cofactor in the development of fibrosis and cirrhosis.
Only methods that allow for the **simultaneous quantification of fat and iron** should be used in order to minimize confounding factors.
Quantifying fat and iron deposits

**MR sequences for fat quantification:**
- Spectroscopy
- Chemical shift – Multiple Echos
  - Opposed-phase / In-phase (OP/IP)
  - mDixon
  - Iterative Decomposition of Water and Fat with Echo Assimetry and Least-Squares Estimation (IDEAL)
  - Multi-echo Chemical Shift (MECSE)

**MR sequences for iron quantification:**
- Gradient-echo for signal intensity ratios calculation
- Chemical shift – Multiple Echos
  - mDixon
  - IDEAL
  - Multi-echo Chemical Shift (MECSE)
Proton Density Fat Fraction (PDFF)

• Different from mass fat fraction because some other parenchyma components do not provide MR signal

• Definition¹: Ratio of density of mobile protons from fat (triglycerides) and the total density of protons from mobile triglycerides and mobile water

\[ \eta_{\text{PDFF}} = \frac{F}{W + F} \]
Proton Density Fat Fraction (PDFF)

Potential confounders:

- T1 bias
- T2* decay
- Multiple fat peaks
- Temperature
- B₀ field
- B₁ field
- Noise bias
- Eddy currents
- Concomitant gradients

Quantifying fat and iron deposits
Multi-echo Chemical Shift Gradient Echo (MECSE)

- Spatial resolution:
  - Plane: Axial
  - In-plane: pixel $\leq 1 \times 1$ mm
  - Slice-thickness: $< 8$ mm
- Flip angle: $10^\circ$
- Echo times: 6 - 12
  - First: 0.99 ms
  - Last: 9.69 ms
  - Spacing: 0.7 – 1.15 ms
- Magnitude and phase reconstruction
- Slices: 34
- Acquisition time: 12-18s

Quantifying fat and iron deposits

Multi-echo Chemical Shift Gradient Echo (MECSE)

- Measured signals (magnitude)

Quantifying fat and iron deposits

Multi-echo Chemical Shift Gradient Echo (MECSE)

• Signal modelling:

$$|S(TE)| = \sqrt{S_w^2 e^{-2R_{2w}^* TE} + S_f^2 e^{-2R_{2f}^* TE} + 2S_w S_f e^{-(R_{2w}^* + R_{2f}^*) TE} \cos(-\omega TE)}$$

Water  Fat  Water-Fat chemical shift

$$\omega = 2\pi f$$

$$f = 210 \text{Hz} \ (1.5T)$$
$$f = 420 \text{Hz} \ (3.0T)$$

Quantifying fat and iron deposits

Multi-echo Chemical Shift Gradient Echo (MECSE)

• However…, there are multiple fat peaks at different frequencies

\[
|S(TE)| = \sqrt{S_w^2 e^{-2 R_w^* TE} + S_f^2 e^{-2 R_f^* TE} + 2 S_w S_f e^{-(R_w^* + R_f^*) TE} \cos(-\omega TE)}
\]

Part of the model extended for a multi-peak modelling
Quantifying fat and iron deposits

Multi-echo Chemical Shift Gradient Echo (MECSE)

\[ |S(TE)| = \sqrt{S_w^2 e^{-2R_{2w}^* TE} + S_f^2 e^{-2R_{2f}^* TE} + 2S_w S_f e^{-(R_{2w}^* - R_{2f}^*) TE}} \cos(-\omega TE) \]

Water Fat Water-Fat chemical shift

Water-Fat (sinusoid)

Iron (exponential)
Quantifying fat and iron deposits

Multi-echo Chemical Shift Gradient Echo (MECSE)

• The calculation of Fat, Water and R2*w components voxelwise allows for the generation of parametric maps
• Non-linear spatial registration is recommended

Case #1
Patient: Histologic steatosis grade 1, iron grade 2

QUIBIM QUANTIFICATION:
PDFF = 8.5%
Fe = 21.3 umol/g

Case #2
Patient: Histologic steatosis grade 1, iron grade 4

QUIBIM QUANTIFICATION:
PDFF = 11%
Fe = 40.8 umol/g

Cases provided by: Dra. Manuela França, Centro Hospitalar do Porto.
Quantifying fibrosis and inflammation
Quantifying fibrosis and inflammation

- MR diffusion
  - It has been proposed as a tool to assess liver inflammation and fibrosis

Quantifying fibrosis and inflammation

- MR diffusion modelling
  - Mono-exponential: ADC
  - Bi-exponential: Intra-voxel incoherent motions (IVIM) to calculate D, D* and f

\[ S_I = S_0 \cdot f \cdot e^{-b \cdot (D+D^*)} + S_0 \cdot (1-f) \cdot e^{-b \cdot D} \]

Perfusion component
Cellularity component

Quantifying fibrosis and inflammation

- MR diffusion
  - ADC and f are related to fibrosis and inflammation, but do not allow to grade patients with specificity

Quantifying fibrosis and inflammation

- **T1**
  - Sensitive to the macromolecular environment in tissues: fibrosis
  - Methods
    - Inversion-Recovery
    - Variable flip angle
  - TE and TR should stay constant for all Flip Angles
  - Same preparation for all flip angles
  - Flip Angles (from 2 to 7 in total), our proposal:
    - 2, 5, 10, 15, 25, 45
  - Number of signal averages >= 2

Quantifying fibrosis and inflammation

Quantifying fibrosis and inflammation

- Virtual Elastography (liver stiffness kPa)
Conclusions
Conclusions

• **Fat and iron** can be appropriately measured simultaneously from *Multi-Echo Chemical Shift Encoded (MECSE)* MR sequences.

• Although *MR diffusion* has been widely evaluated to diagnose and monitor liver *fibrosis and inflammation*, it is **not capable** to differentiate between grades.

• **T1 mapping** is **promising** to extract fibrosis and inflammation features.

• New methods like *Virtual Elastography* add insights into the value of Imaging Biomarkers in diffuse liver diseases.
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