Proton-density fat fraction-derived R2* liver iron concentration – an exploratory study of Revita-2 phase II trial data

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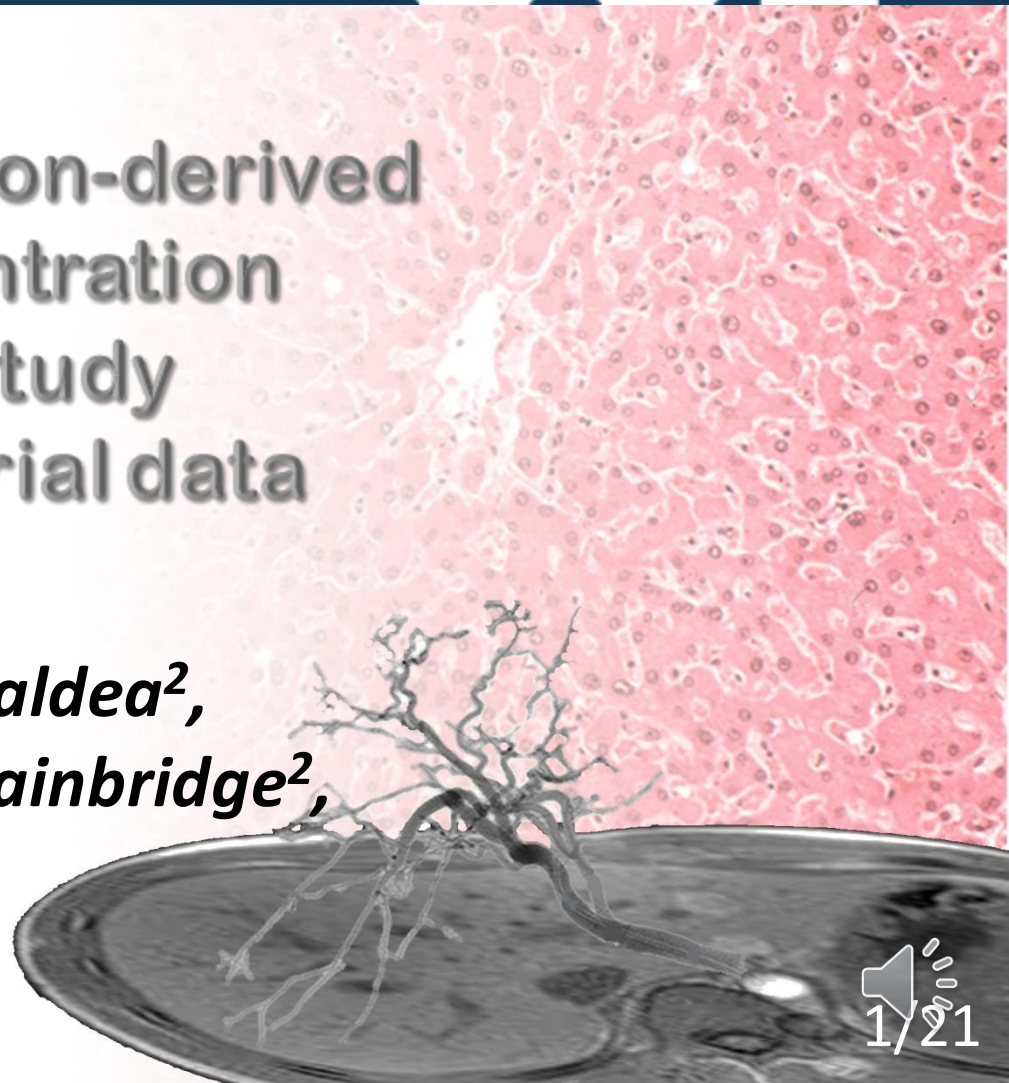


Declaration of Financial Interests or Relationships

Speaker Names: Kelly White, Juan-Carlos Lopez Talavera

Have the following financial interest or relationship(s) to disclose with regard to the subject matter of this presentation:

- Employment: full-time employees of Fractyl Laboratories Inc and may hold Fractyl stock and/or stock options.

Speaker Names: Manil D Chouhan, Naomi Sakai, Francisco Torrealdea, Alan Bainbridge, Stuart A Taylor

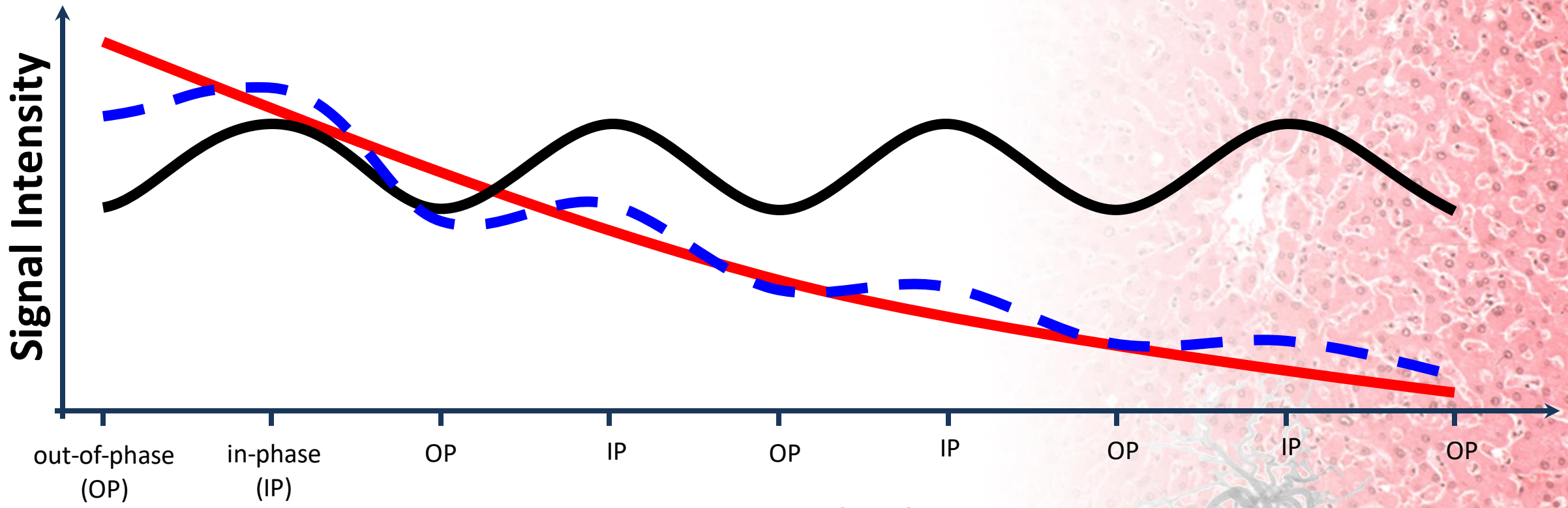
Have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Introduction – MRI-PDFF and LIC measurement

- Use of MRI-based proton density fat fraction (PDFF) measurements of liver fat for clinical trial primary endpoints is well established.

- Accuracy of PDFF liver fat fraction measurements is reliant on correction for T2/T2* related signal decay

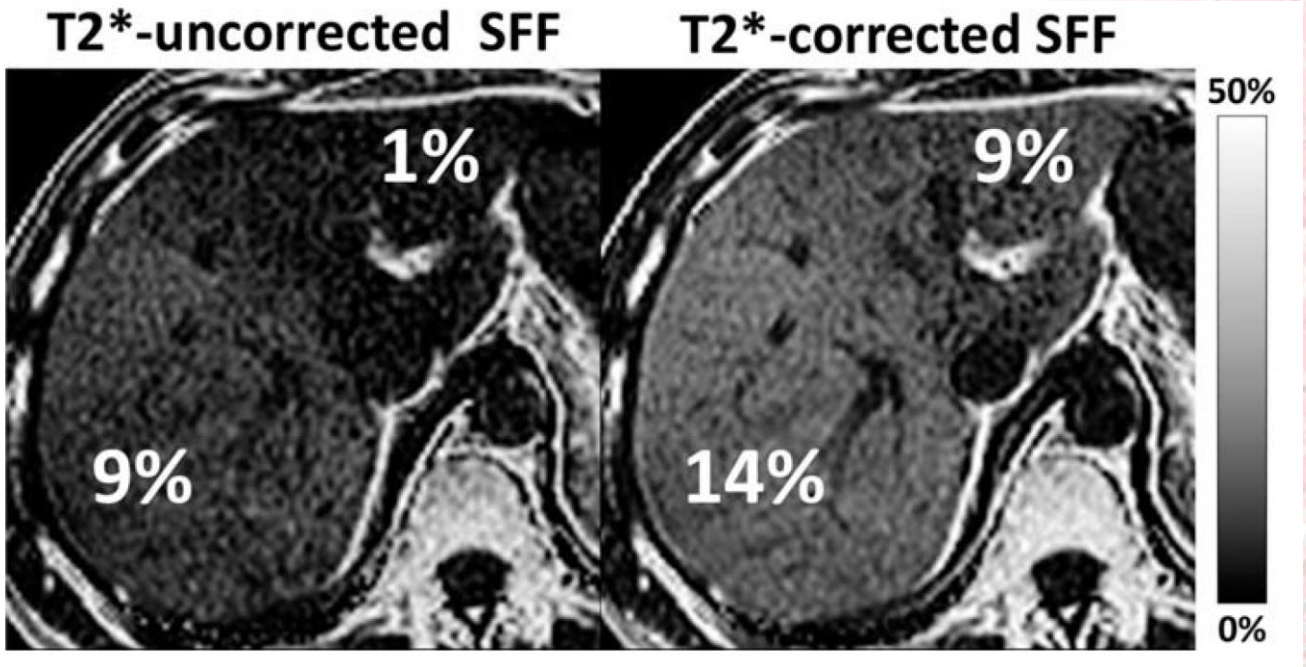
Introduction – MRI-PDFF and LIC measurement



(adapted from Sirlin CB, 'Hepatic Steatosis - Liver MR Imaging: Quantitative Approaches to Liver Disease', ISMRM Hawaii, 2017.)

Introduction – MRI-PDFF and LIC measurement

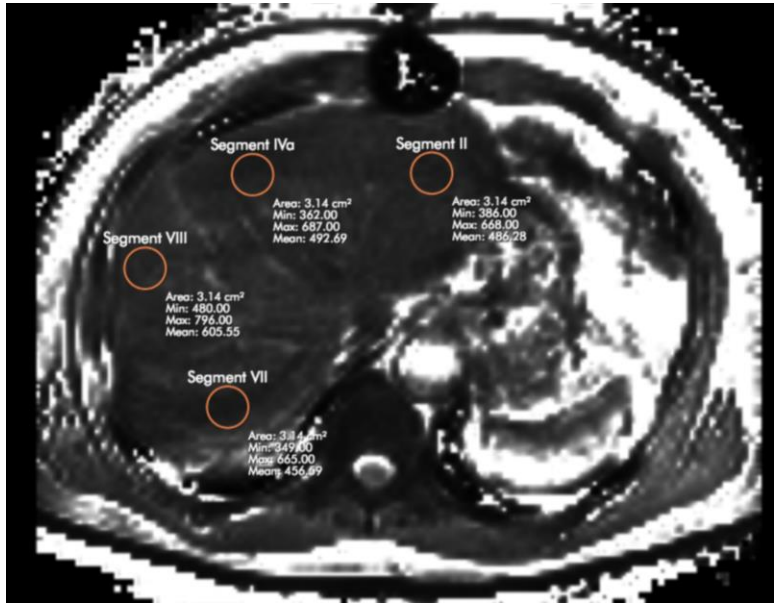
- Multi-echo data can be modelled to generate T2* maps, for FF map correction:

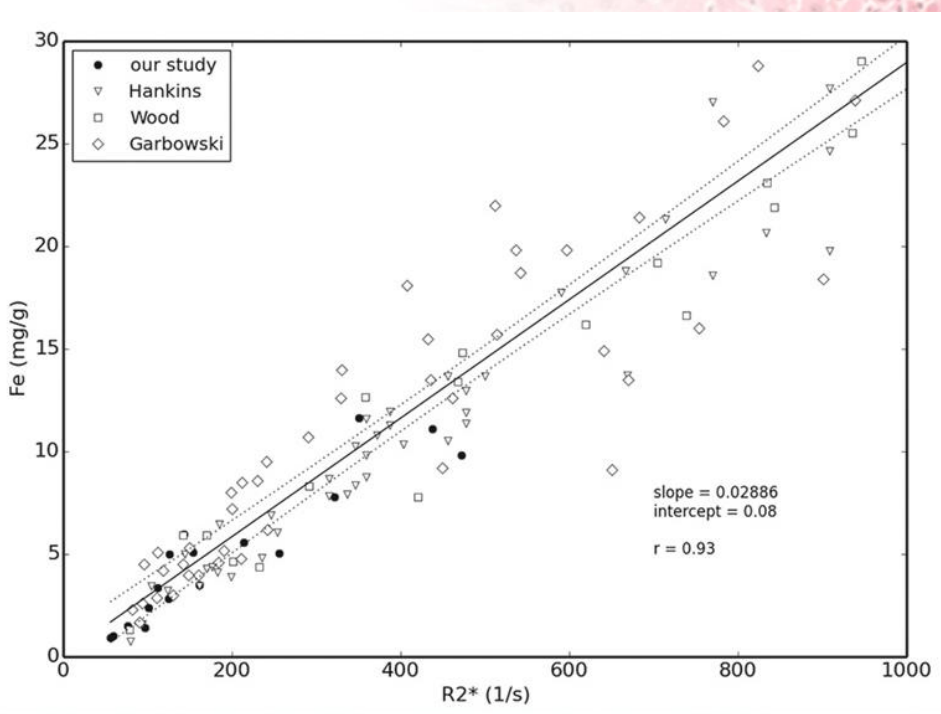


(from Reeder SB et al. J Magn Reson Imaging. 2011;34(4):729-749.)

Introduction – MRI-PDFF and LIC measurement

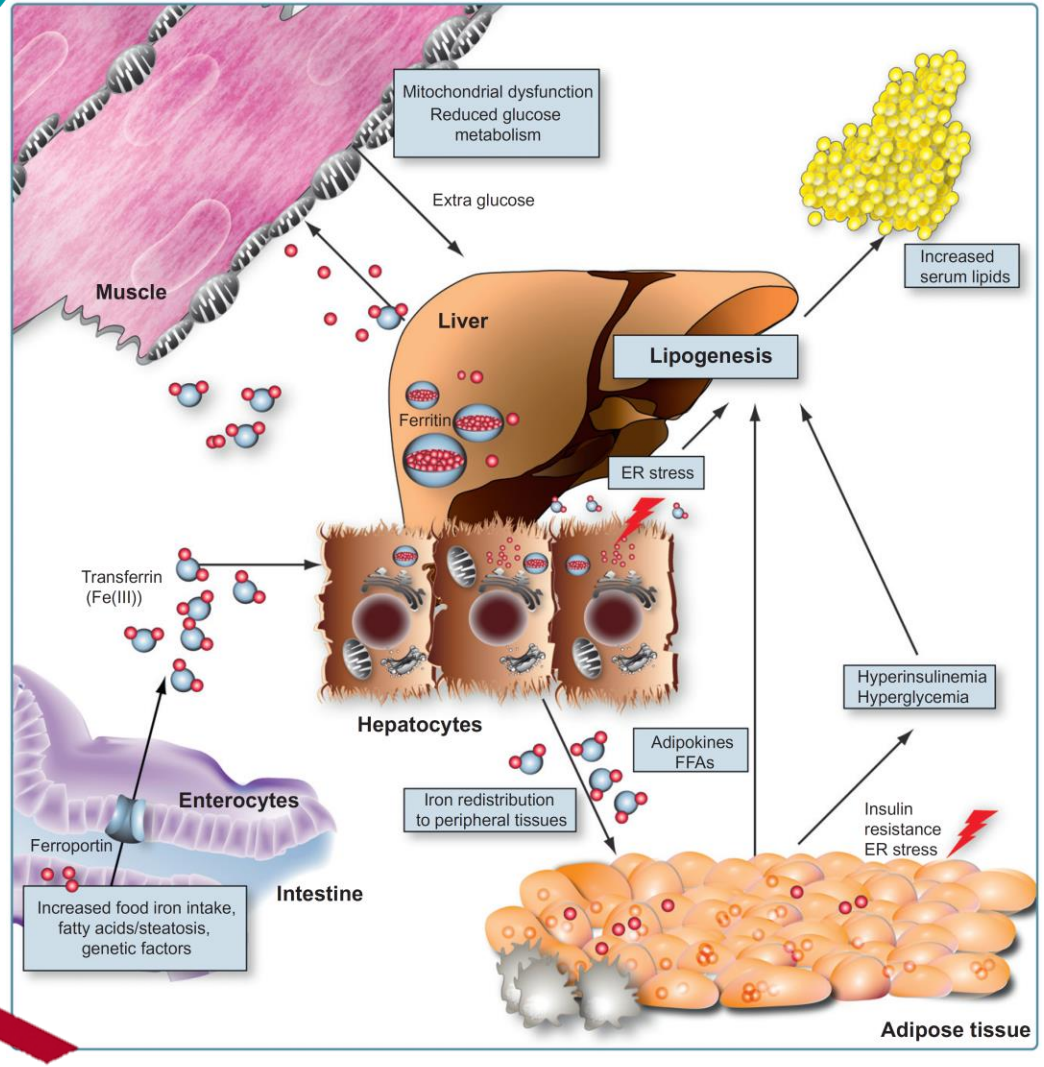
- T2* maps are generated as part of the PDFF measurements and can be used to estimate liver iron concentration (LIC).





(from Henninger B et al. RöFo. 2015;187(06):472-479, for measurements at 1.5T.)

Introduction – MRI-PDFF and LIC measurement

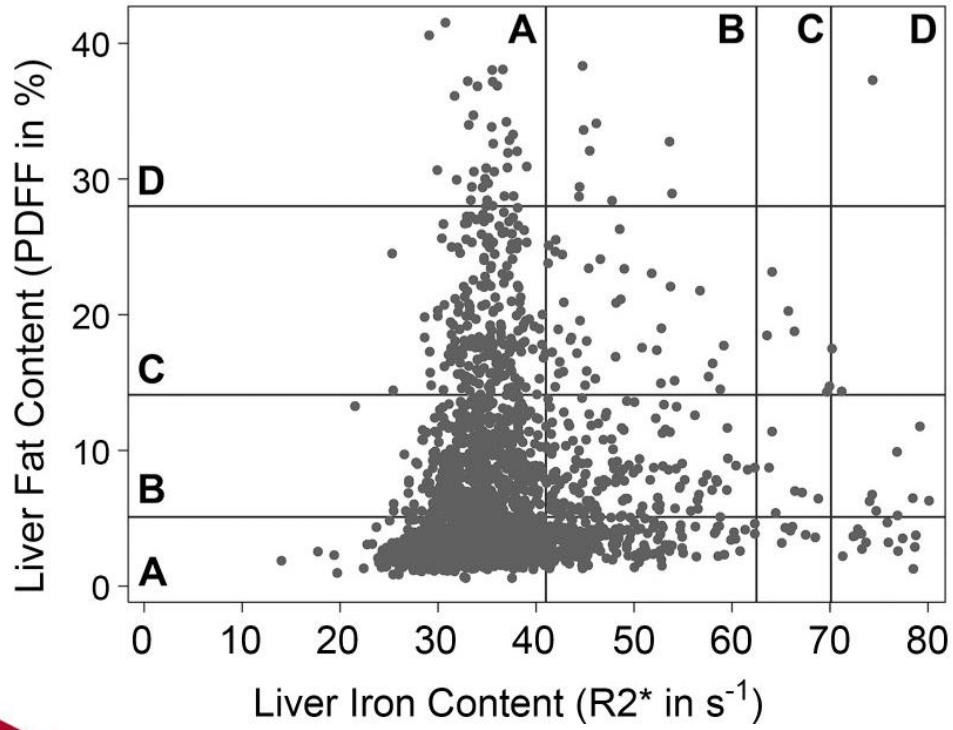


(from Dongiovanni P et al. *J Hepatol*. 2011;55(4):920-932.)

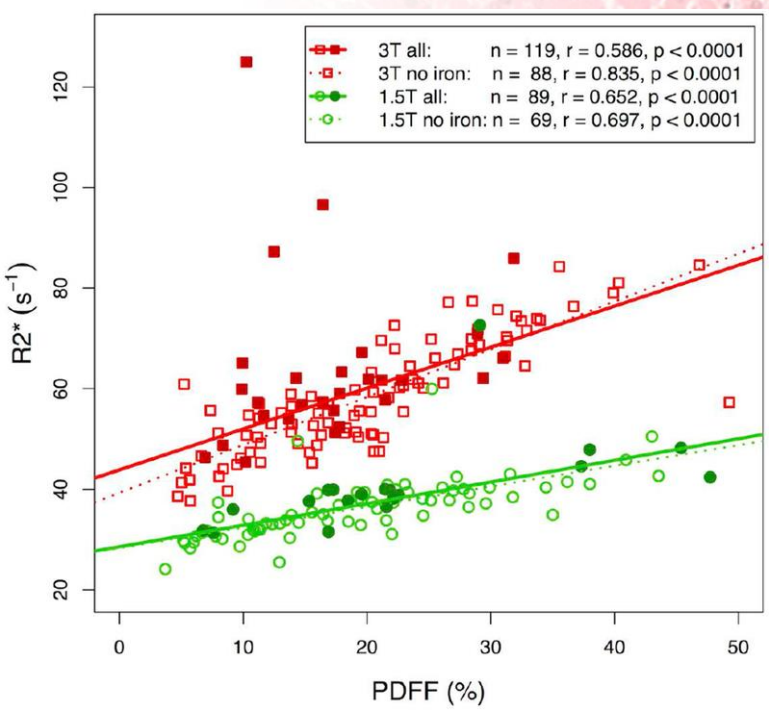
- Dysregulation of iron homeostasis has been associated with:
  - non-alcoholic fatty liver disease (NAFLD)
  - and type 2 diabetes mellitus (T2DM)

Introduction – MRI-PDFF and LIC measurement

- The value of PDFF-derived T2*/R2* for quantification of LIC across varying siderosis/steatosis is under ongoing investigation



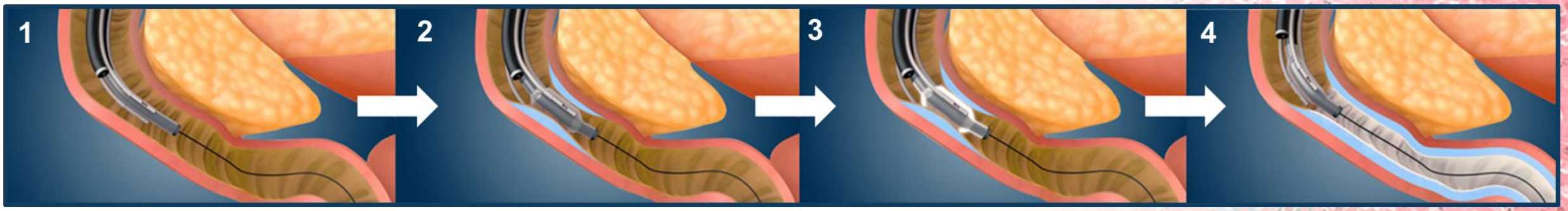
(from Kühn J-P et al. *Radiology*. 2017;284(3):706-716.)



(from Bashir MR et al. *J Magn Reson Imaging*. 2019;49(5):1456-1466.)

Introduction – the Revita-2 study

- DMR is an endoscopic treatment designed to reduce insulin resistance and hyperinsulinemia[1,2]
- Prior studies (Revita-1) showed a single DMR procedure improves hepatic and glycemic parameters through 2 years in patients with T2DM, indicating potential benefit in T2DM ± NAFLD/NASH[3-6]



FRACTYL

1. Hadefi A et al., *Dig Dis*. 2018;36:321-324.2. Rajagopalan H et al., *Diabetes Care*. 2016. 3. Cherrington A et al., *Gastrointest Endoscopy Clin N Am*. 2017;27:299-311. 4. Van Baar A et al., *Gut*. 2019; pii:gutjnl-2019-318349. 5. Haidry R et al., *GIE*. 2019;673 - 681.e2. 6. van Baar ACG et al., DTM 2019 poster VAN 19122D.
REVITA-2 NCT02879383; DMR = duodenal mucosal resurfacing; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; T2D = type 2 diabetes.

Introduction – the Revita-2 study

- Revita-2 is a blinded, sham-controlled international multi-site multi-scanner vendor cross-over trial (NCT02879383).
- Investigation of the effect of DMR on hepatic and glycaemic parameters in patients with poorly controlled T2DM
- Trial endpoints include absolute and relative change in liver MRI-PDFF from baseline at 12 weeks (in patients with MRI-PDFF >5% at baseline)

Aims

1. To explore the association between PDFF-derived R2* LIC measurements and liver FF

2. To determine if there is a difference in the strength of association between relative change in FF and LIC at 12 weeks:

   in DMR and sham-treatment cohorts

   to support the presence of any treatment-induced mechanistic differences in hepatic iron metabolism

Methods – Image acquisition

- Patients recruited at 8 EU sites
- Data were acquired at 7 sites (4 Philips & 1 GE 3T system, 1 Philips & 1 GE 1.5T system).
- Vendor-derived PDFF sequences (e.g. Philips mDixonQuant, GE IDEAL-IQ) were used

Parameter	Philips	GE
PDFF manufacturer-supplied package	mDixon Quant	IDEAL IQ
Sequence variant	3D Spoiled Gradient Echo	3D Spoiled Gradient Echo
Imaging Time	Breath-hold (< 20s)	Breath-hold (< 20s)
3D Slab dimensions*	40 Axial slices FH – 240 mm RL – 400 mm AP – 350 mm	40 Axial Slices FH – 240 mm Freq FoV: 400 mm Phase FoV: 0.88
Voxel Dimensions	6 mm axial slices 2-2.5 mm isotropic in plane	6 mm axial slices 2-2.5 mm isotropic in plane
TR	Shortest (5-10 ms)	Shortest (5-10 ms)
Number of echoes	6	6
TE of first echo	Shortest (~1-2ms)	Shortest (~1-2ms)
Echo spacing	Shortest (~1-2ms)	Shortest (~1-2ms)
Flip Angle	3 degrees	3 degrees
Parallel Imagaing Factor	2	2
Number of averages	1	0.5
Number of shots	-	2
Reconstructed images	Fat-only image Water-only image PDFF map T2* map	Fat-only image Water-only image PDFF map T2* map

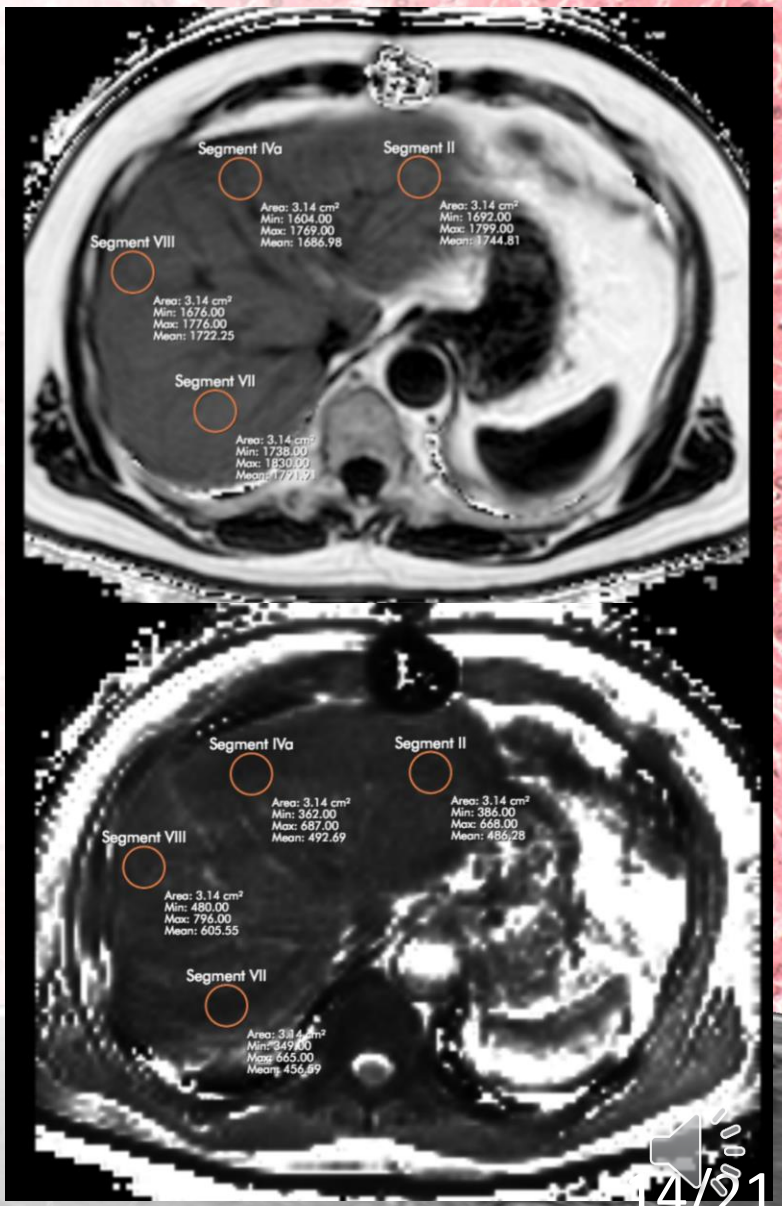
Methods – Study cohort

Baseline and 12-week post-treatment liver MRI scans

- initial open-label training (n=17) cohort
- DMR (n=39) cohort
- Sham (n=23) cohort

Methods – Image analysis

- Custom-developed online platform (Ambra Health, New York, USA)
- Circular ROIs measuring upto 20mm diameter
- Colocalised on PDFF maps and T2* maps
- LIC (µmol/g) estimated from T2* data using previously reported methods[1]



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Methods – Statistics

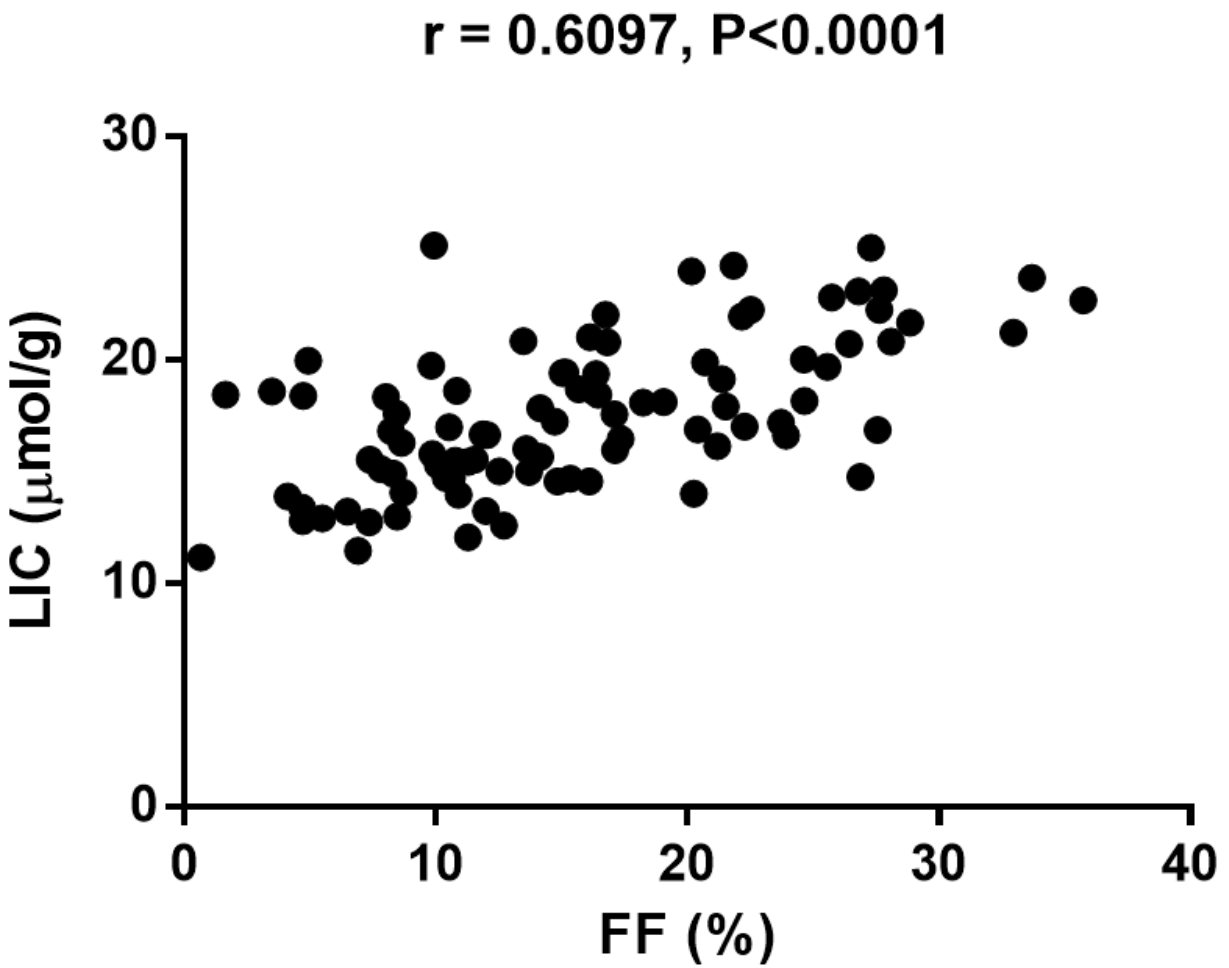
- Linear regression with calculation of Pearson's correlation coefficient

- Relationship assessed:

  a) Between baseline absolute liver FF and LIC measurements

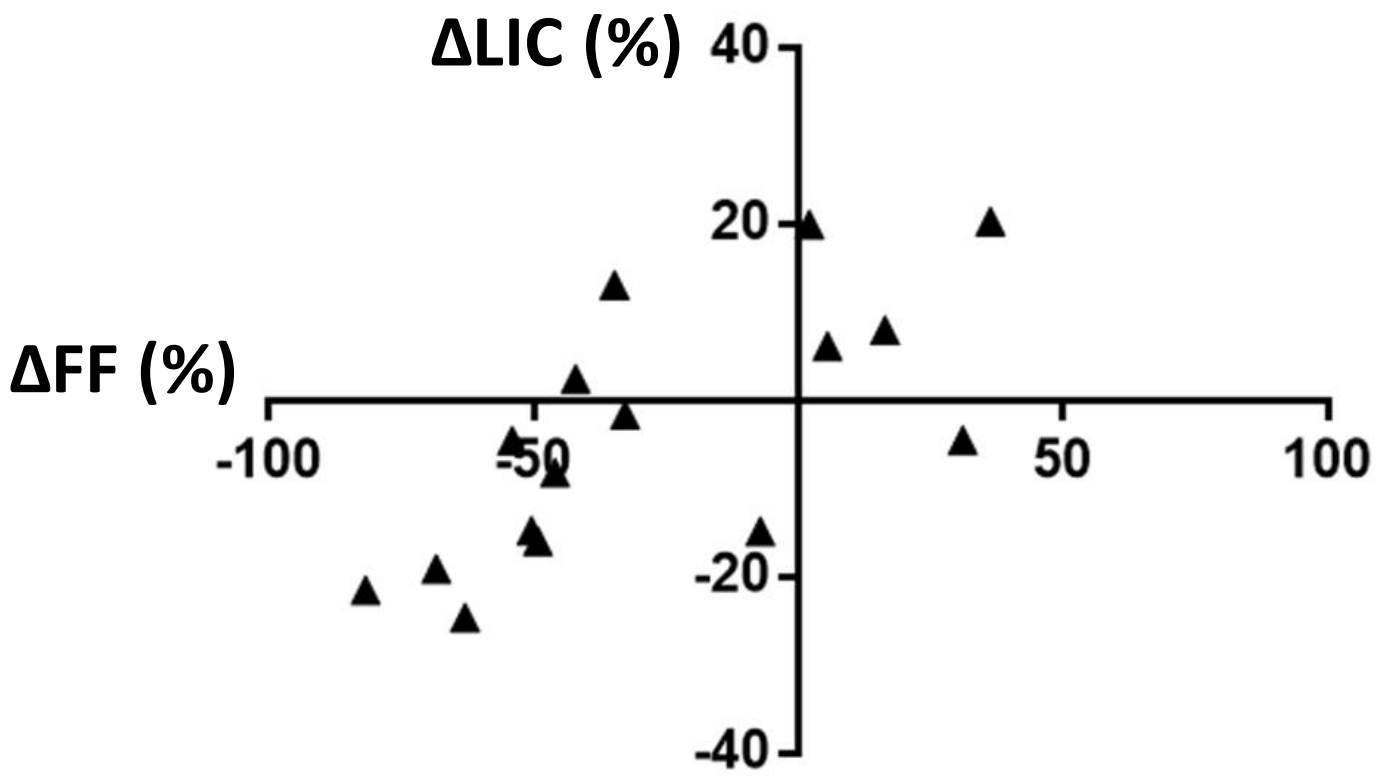
  b) Between relative (%) change in liver FF and LIC at 12 weeks post-treatment

Results – Baseline correlation



Results – Training case cohort

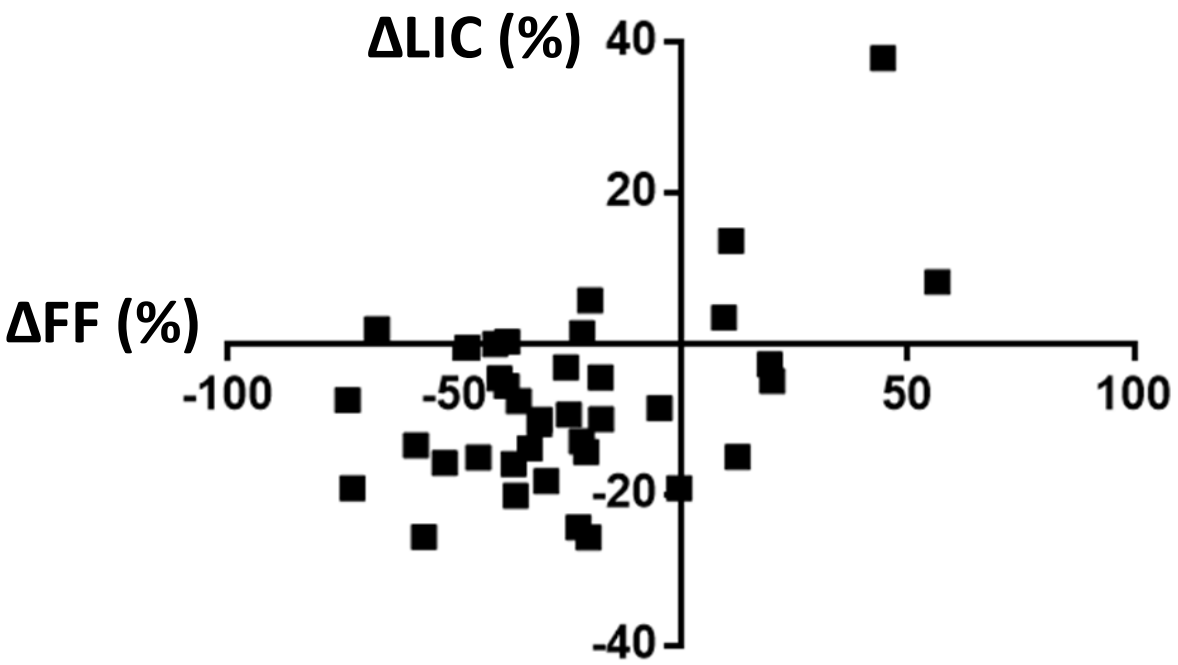
r = 0.7025, P=0.0024



Results – DMR vs Sham cohort

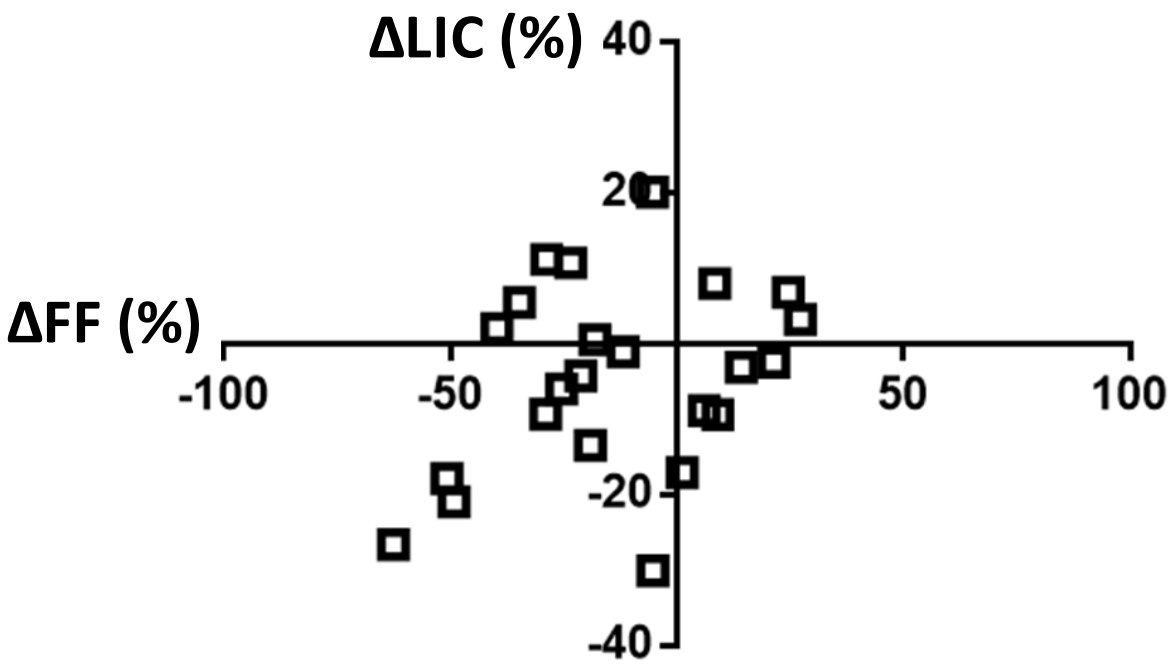
DMR

r = 0.4943, P=0.0016



Sham

r = 0.3235, P=0.1322



Discussion

- The significant positive correlation demonstrated between PDFF-derived liver FF and LIC is comparable with previously reported results[1]

- This finding is important, given that data has been collated from multiple field strengths and patients with normal range LIC levels (<36 µmol/g)[2]

1. Bashir, M. R. et al. Hepatic R2* is more strongly associated with proton density fat fraction than histologic liver iron scores in patients with nonalcoholic fatty liver disease. J. Magn. Reson. Imaging 49, 1456–1466 (2019).

2. Alústiza Echeverría, J. M., Castiella, A. & Emparanza, J. I. Quantification of iron concentration in the liver by MRI. Insights Imaging 3, 173–80 (2012).

Discussion

- Significant linear correlations between post-treatment relative (%) change in liver FF and LIC in both training and DMR cohorts were noted

- Weaker non-significant correlations in the sham cohort raise the possibility of altered mechanistic effects on hepatic iron metabolism as a result of treatment.

- To better understand this phenomenon, ongoing studies using non-imaging biomarkers of iron metabolism are underway.

Conclusions

- PDFF-derived liver FF and LIC are positively correlated at baseline.

- Relative change in liver FF and LIC at 12 weeks is more strongly correlated post-DMR than in sham-treated patients raising the possibility of altered mechanistic effects on hepatic iron metabolism as a result of DMR.

Questions?

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