Serum ferritin levels in patients with non-elevated Proton-Density Fat Fraction-derived R2* Liver Iron Concentration – an exploratory study of Revita-2 phase II trial data –

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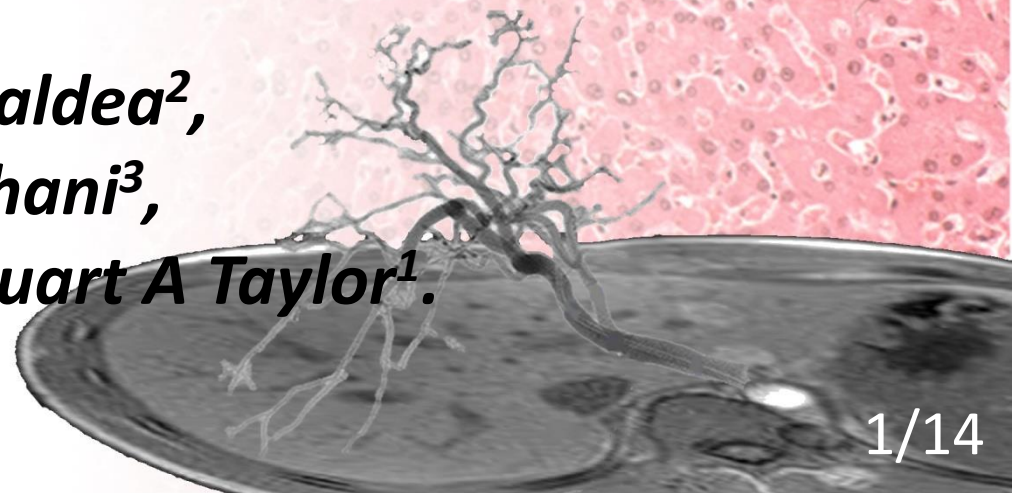
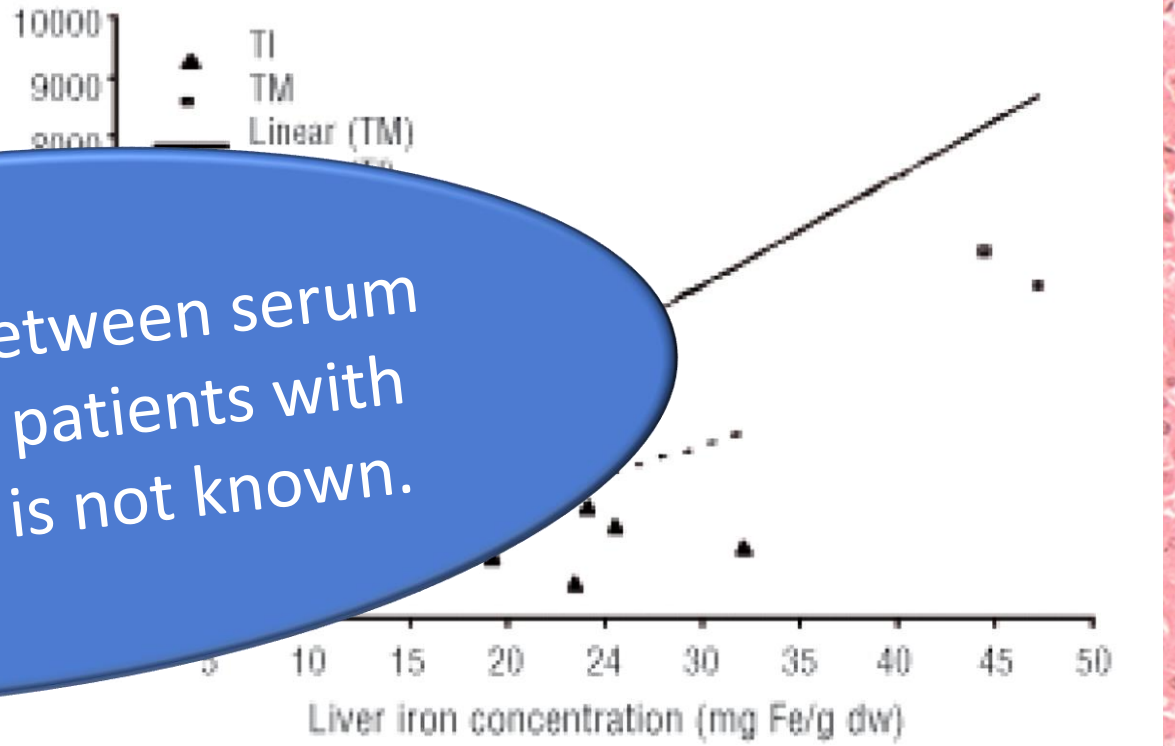


Background – Serum ferritin and liver iron concentration

- Dysregulation of iron homeostasis has been associated with fatty liver disease and type 2 diabetes mellitus (T2DM)[1]
- Serum ferriti
  correlated wi
  concentration (

The relationship between serum ferritin and LIC in patients with non-elevated LIC is not known.



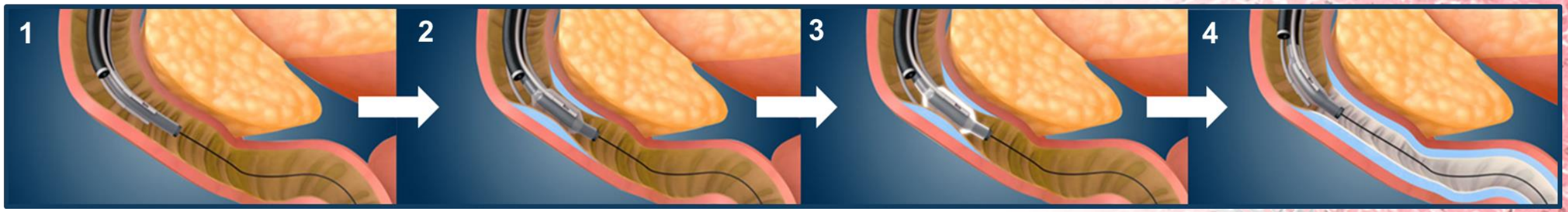
1. Fernández-Real, J. M. & Manco, M. Effects of iron overload on chronic metabolic diseases. Lancet Diabetes Endocrinol. 2, 513–526 (2014)
2. Taher et al. Correlation of liver iron concentration determined by R2 magnetic resonance imaging with serum ferritin in patients with thalassemia intermedia. Haematologica 2008 93: 1584-1586.

Background – MRI-PDFF

- MRI-based proton density fat fraction (PDFF) can be used to quantify liver fat.
- T2* maps are generated as part of the PDFF measurements and can be used to estimate liver iron concentration (LIC).
- Vendor-derived PDFF sequences (e.g. Philips mDixonQuant, GE IDEAL-IQ) enable multi-site, multi-vendor, multi-field strength studies

Background – Duodenal Mucosal Resurfacing

- DMR catheter is designed to perform submucosal lift and hydrothermal ablation of hyperplastic duodenal mucosa, promote healthy epithelial regrowth within 12 weeks, and reduce insulin resistance and hyperinsulinemia[1,2]



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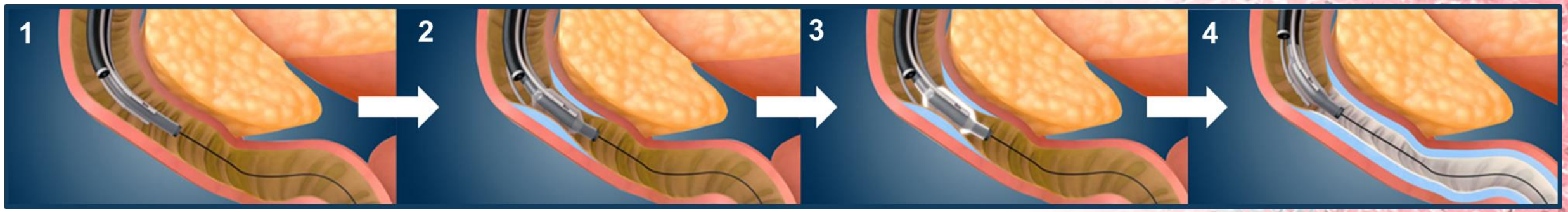
1. Hadefi A et al., *Dig Dis*. 2018;36:322-324.2. Rajagopalan H et al., *Diabetes Care*. 2016. 3. Cherrington A et al., *Gastrointest Endoscopy Clin N Am*. 2017;27:299-311. 4. Van Baar A et al., *Gut*. 2019; pii: gutjnl-2019-318349. 5. Haidry R et al., *GIE*. 2019; 673 - 681.e2. 6. van Baar ACG et al., DTM 2019 poster VAN 19122D.
REVITA-2 NCT02879383; DMR = duodenal mucosal resurfacing; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; T2D = type 2 diabetes.

Background – Duodenal Mucosal Resurfacing

- DMR is a well-tolerated procedure with few, self-limited side effects[3-5]
- Prior studies (eg, REVITA-1) showed a single DMR procedure durably improves hepatic and glycemic parameters through 2 years in patients with T2D, indicating potential benefit in T2D with concomitant NAFLD/NASH[3-6]



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1. Hadefi A et al., *Dig Dis*. 2018;36:322-324.2. 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.
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Background – REVITA-2

- Revita-2 is a phase II 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 sub-optimally controlled T2D across 7 sites (5 in EU, 2 in Brazil)

- Trial endpoints include absolute and relative change in liver MRI-PDFF from baseline at 12 weeks (in patients with MRI-PDFF >5% at baseline)

Purpose

To investigate the relationship between
serum ferritin levels and *non-elevated* proton-density fat fraction (PDFF) derived
R2* liver iron concentration (LIC) in patients with T2DM
undergoing endoscopic Duodenal Mucosal Resurfacing (DMR).

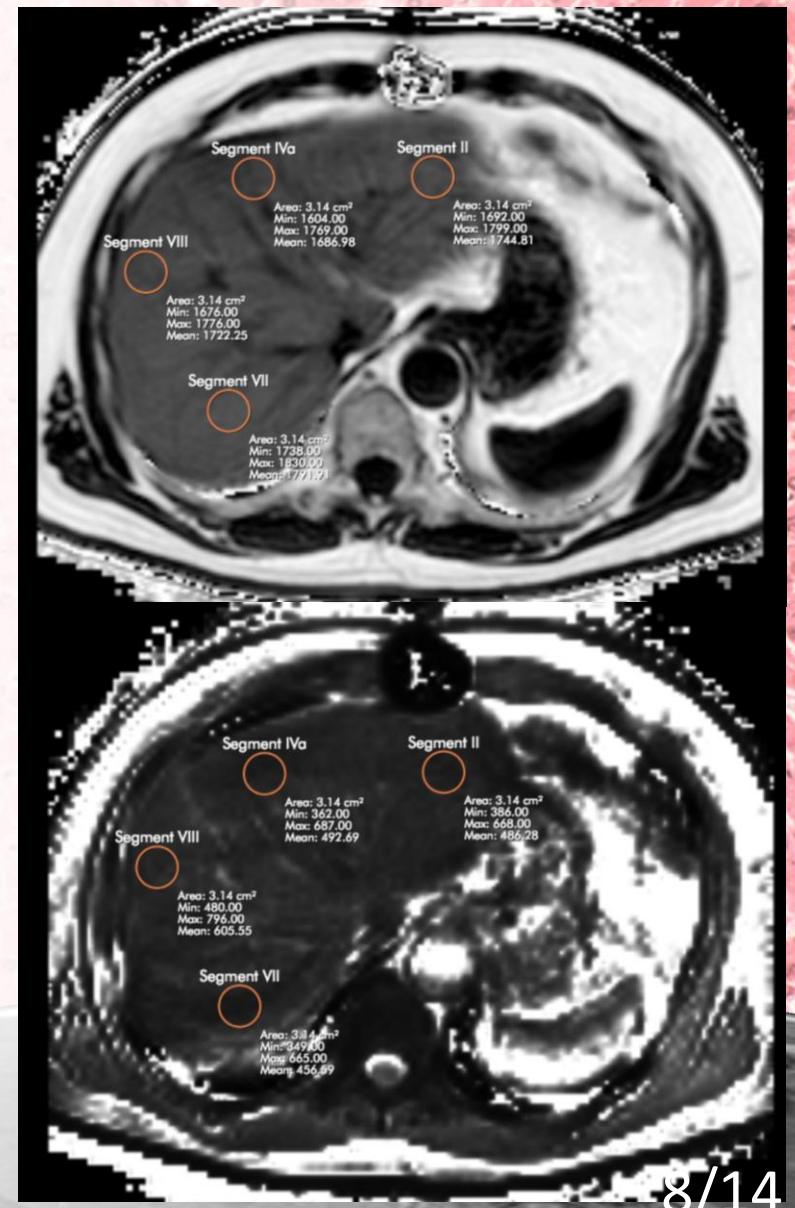
Materials and methods – REVITA-2 – Image acquisition

- Vendor-derived PDFF sequences (e.g. Philips mDixonQuant, GE IDEAL-IQ) were used for multi-site, multi-vendor, multi-field strength studies

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

Materials and methods – REVITA-2 – 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 as previously[1]
- Absolute and relative (% of baseline) within-subject change in liver FF and LIC were assessed



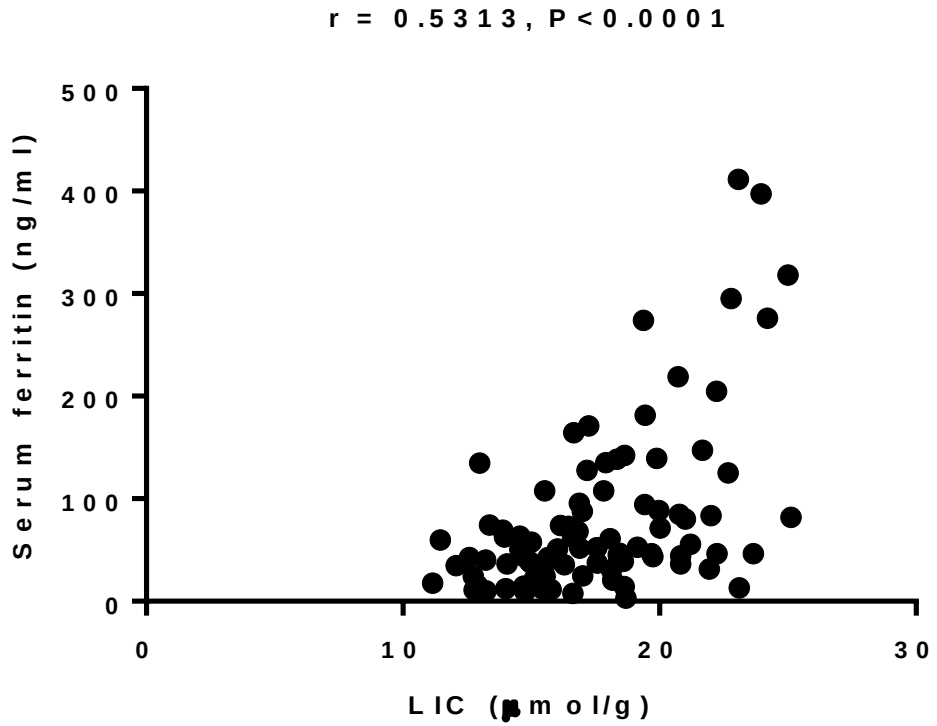
1. Paisant, A., d'Assignies, G., Bannier, E., Bardou-Jacquet, E. & Gandon, Y. MRI for the measurement of liver iron content, and for the diagnosis and follow-up of iron overload disorders. Press. Medicale 46, e279–e287 (2017).

Results – Study cohort

Baseline and 12-week post-treatment liver MRI scans with paired serum ferritin levels for

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

Results – baseline serum ferritin and LIC



- At baseline, a modest positive but significant correlation was demonstrated between LIC and serum ferritin
- All LIC measurements were <32 µmol/g consistent with normal (non-elevated liver iron)[1,2]

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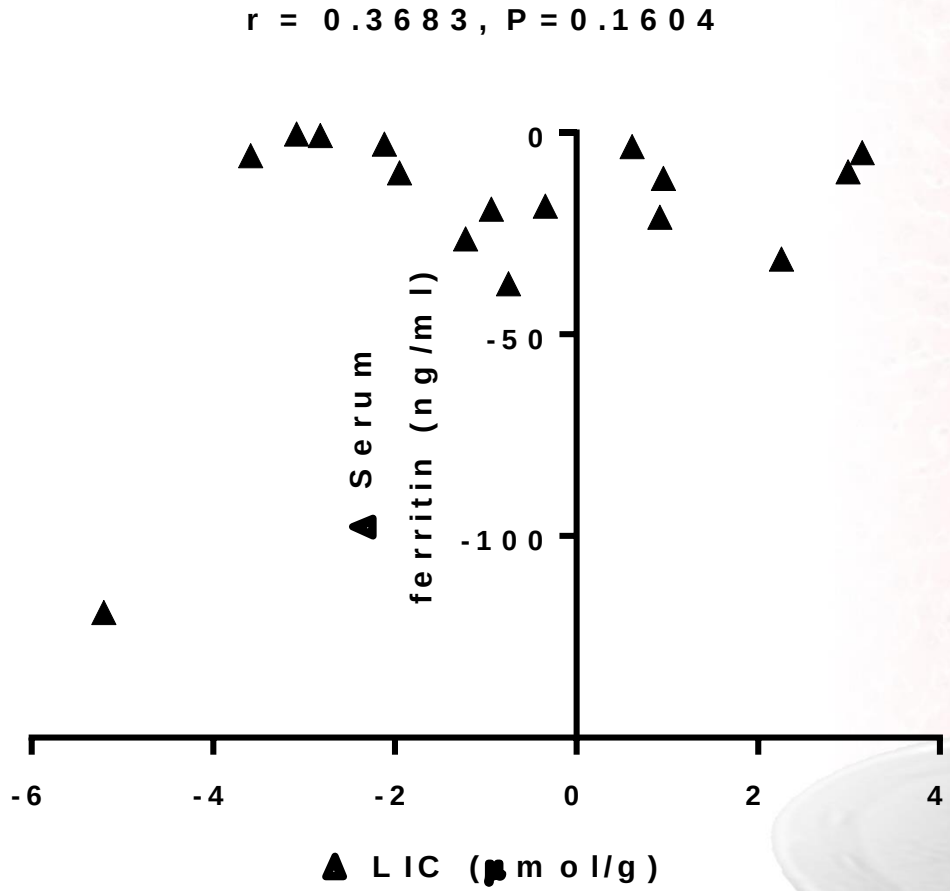
2. St. Pierre TG, Clark PR, Chua-Anusorn W, et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood*. 2005;105(2):855–861.)

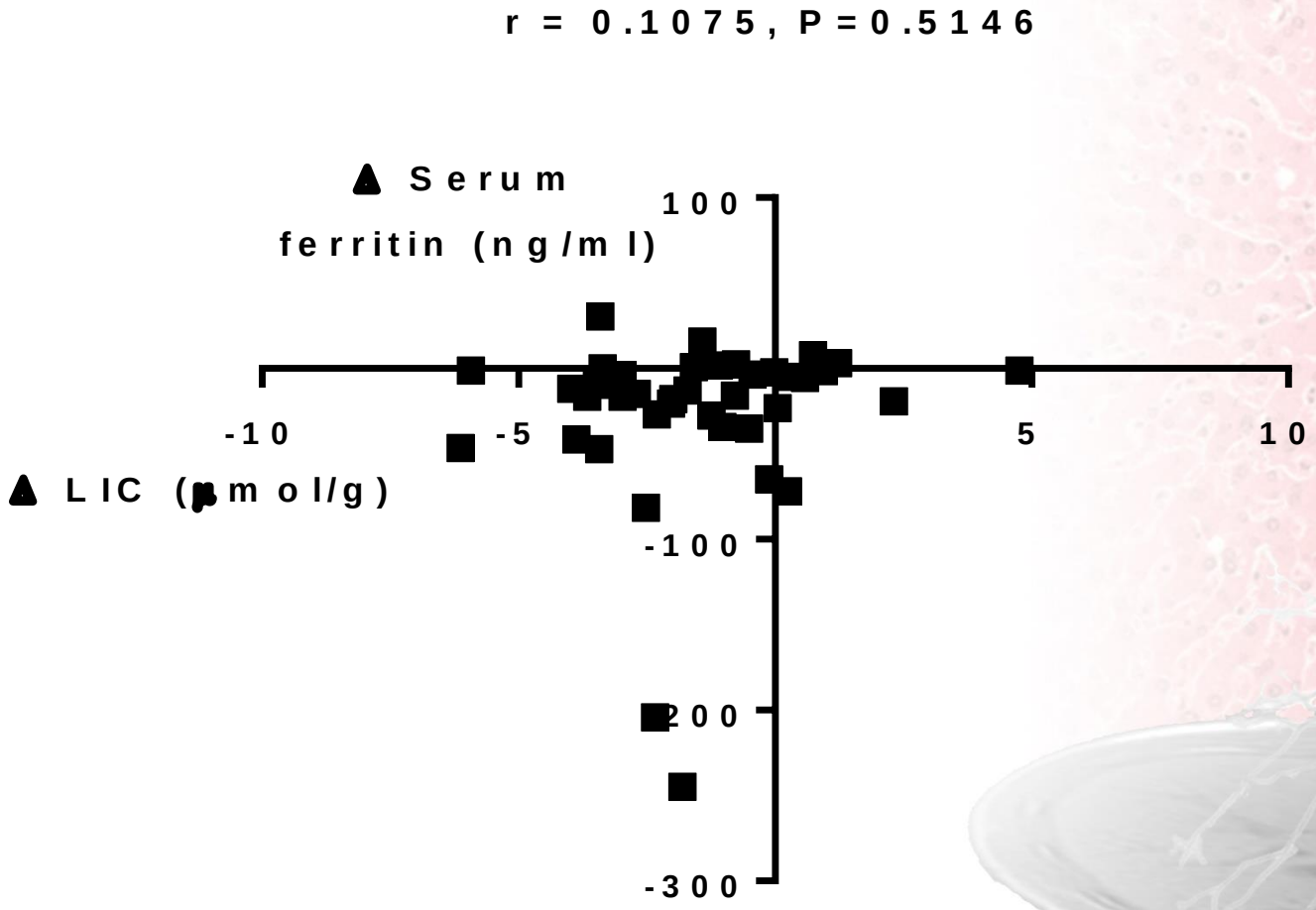
Results – post-treatment change in serum ferritin and LIC

Open-label training cohort (n=17) – change in serum ferritin vs change in LIC 12 weeks post-treatment



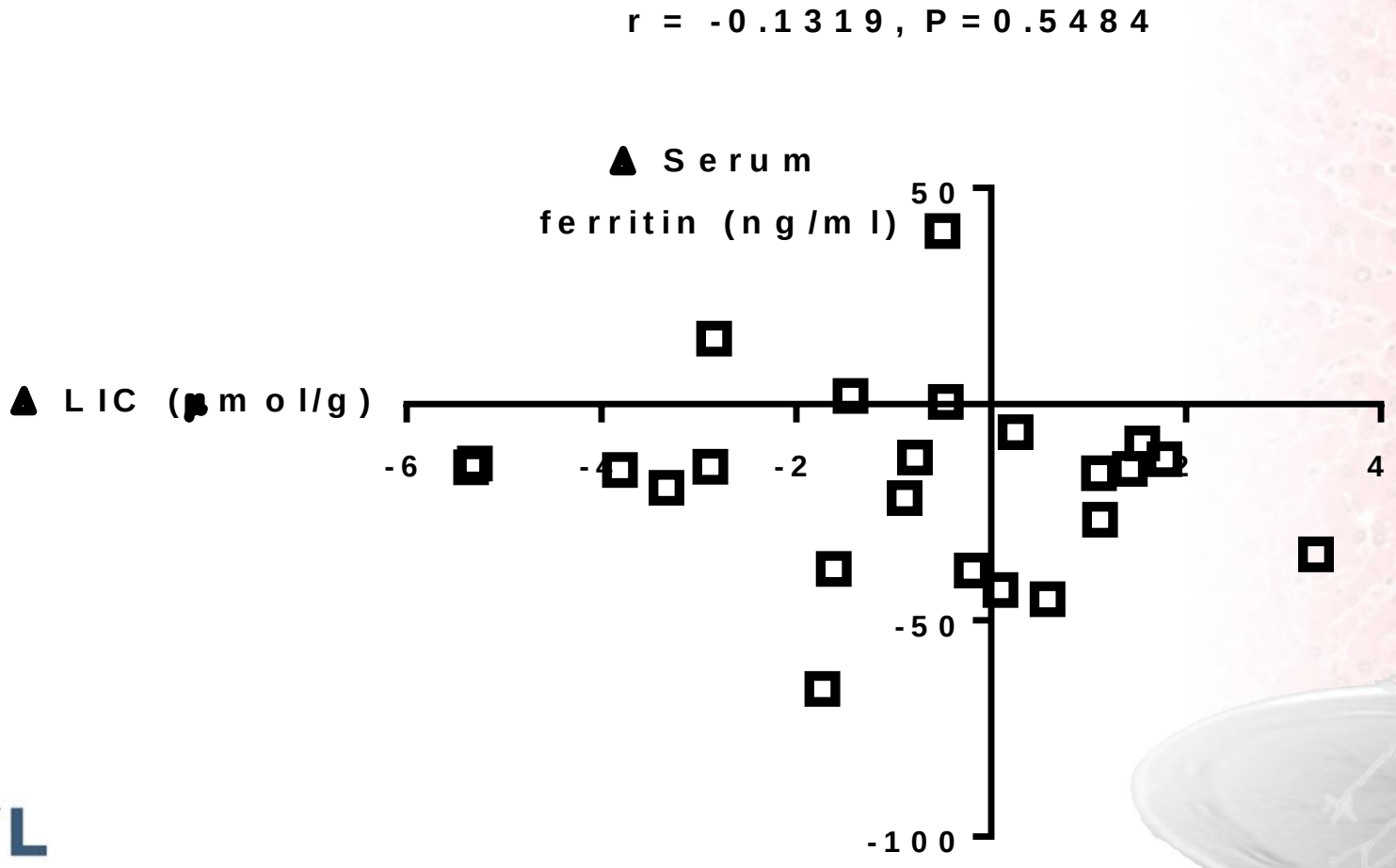
Results – post-treatment change in serum ferritin and LIC

DMR cohort (n=39) – change in serum ferritin vs change in LIC 12 weeks post-treatment



Results – post-treatment change in serum ferritin and LIC

Sham treatment cohort (n=23) – change in serum ferritin vs change in LIC 12 weeks post-treatment



Conclusion

- Even at non-elevated LIC levels, serum ferritin and LIC are positively correlated.

- Poor correlations in LIC and serum ferritin in post-treatment changes may reflect mechanistic effects on hepatic iron metabolism as a result of DMR.