Role of Iron in ASH/NASH

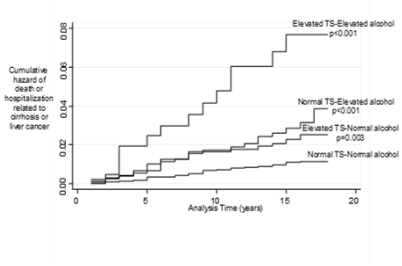
Kris V. Kowdley MD
Director, Liver Center of Excellence
Virginia Mason Medical Center
Clinical Professor of Medicine
University of Washington
Seattle, WA

Alcohol Consumption and Iron Stores: NHANES III

	Prevalence (%) (and SE) in the following alcohol consumption categories (in drinks/day): None¶	0-1	1-2	>2	Adjusted* OR: 0-1 Vs none	1-2 Vs none	>2 Vs none
Ferritin>300 (men) or Ferritin>200 (women)	**8.6 (0.5)**	**8.9 (0.7)**	**11.8 (1.4)**	**17.5 (1.8)**	**1.2 (0.96 -1.5)**	**1.4 (0.99 -2.1)**	**1.9 (1.4-2.8)**
TS>45%	**4.5 (0.4)**	**7.2 (0.5)**	**7.4 (1.2)**	**12.5 (1.9)**	**1.4 (1.04 -1.9)**	**1.4 (0.92 -2.0)**	**2.3 (1.7-3.2)**

Ioannou et al., Gastroenterology 2004

Death or hospitalization for cirrhosis or liver cancer vs TS and alcohol intake



Ioannou et al., Clin Gastroenterol Hepatol, 2007

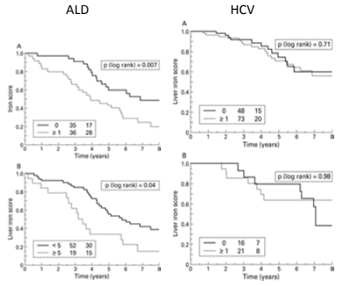
Iron and Insulin-Resistance Syndrome

- 161 non-C282Y +/+ with iron overload
- IRS defined as:
  - BMI>25
  - Type 2 diabetes
  - Hyperlipidemia
- HIC 38-334 μmol/g dry weight
- HII 0.5-4.8
- 94% met criteria for IRS

Mendler et al., Gastroenterol 1999

Iron and survival in ALD

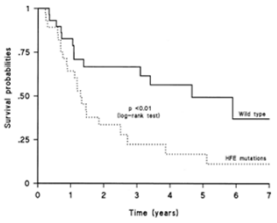
- 229 patients with ALD or HCV followed 1987-93
- Effect of HHIC on survival and HCC
- No relationship between HHIC and risk of HCC
- HHIC predictive of survival in ALD



Ganne-Carrie et al., Gut 2000;46:277-82

HFE mutations and Survival after Resection for HCC

- 61 patients with HCC
- 6 C282Y homozygotes
- 4 C282Y heterozygotes
- 20 H63D heterozygotes
- Improved survival in *HFE wt* patients
- HR 0.42 (0.21-0.8) after controlling for:
  - Age, gender, capsule, number, Okuda stage, Edmonson grade, co-morbid factors



Pirisi et al.,Cancer Vol.89, 2 Pages: 297-302

Iron, *HFE* and NASH

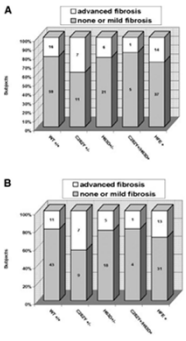
- Pathogenic role for iron highly plausible
- Serum ferritin markedly elevated
- May be associated with type 2 DM
- *HFE* mutations associated with iron loading
- Independent role for HFE mutations unclear
- Referral, selection biases are problems
- Iron depletion may have a role in therapy

Iron, *HFE* and NASH

- Mild to moderate iron overload common in patients with nonalcoholic steatohepatitis (NASH) and “dysmetabolic syndrome”
- Iron overload may contribute to the pathophysiology of NASH
- Previous studies have found conflicting results on this relationship

Advanced fibrosis in NASH patients

- Trend toward association of the heterozygous C282Y mutation (C282Y±) with advanced hepatic fibrosis (OR 2.35, 95% CI 0.82-6.75 [*P* = 0.112])
- Stronger among Caucasians alone (n = 98) (OR 2.97, 95% CI 0.97-9.14 [*P* = 0.057]
- Multiple logistic regression modeling adjusting for age, sex, ethnicity, body mass index, *HFE* genotype status
- Diabetes mellitus was the only independent predictor of advanced hepatic fibrosis (OR 4.37, 95% CI 1.41-13.54 [*P* = 0.010]).



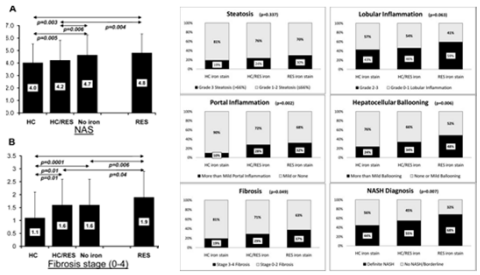
A) Entire cohort

B) Caucasians

P=0.05 between C282Y+/- and wt patients

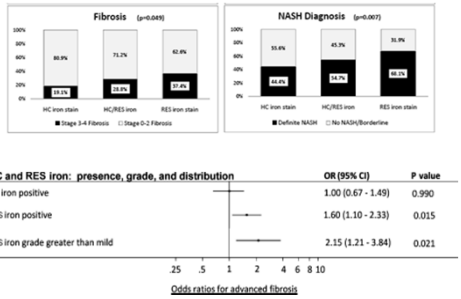
Nelson et al.,Hepatology 2007

Pattern of Iron Deposition and NAFLD Severity



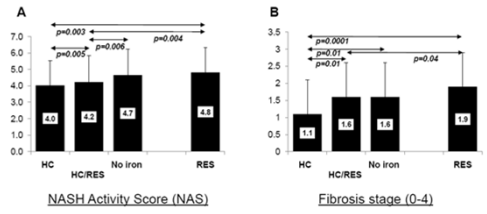
Nelson et al., Hepatology 2011

Pattern of Iron Staining and NASH



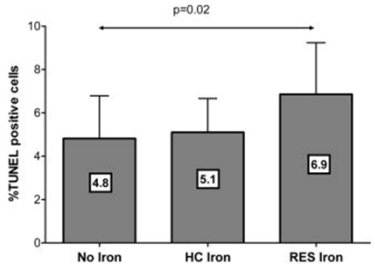
Nelson et al., Hepatology 2011

Iron Staining Pattern and NASH



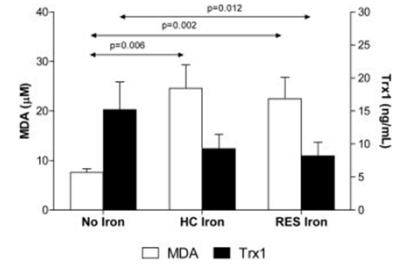
Nelson et al., Hepatology 2011

Hepatic reticuloendothelial system cell iron deposition is associated with increased apoptosis in nonalcoholic fatty liver disease



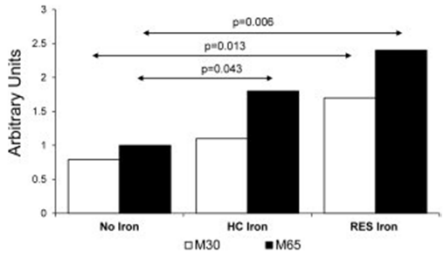
Hepatology
Volume 57, Issue 5, pages 1806-1813, 14 MAR 2013 DOI: 10.1002/hep.26238
http://onlinelibrary.wiley.com/doi/10.1002/hep.26238/full#fig1

Hepatic reticuloendothelial system cell iron deposition is associated with increased apoptosis in nonalcoholic fatty liver disease



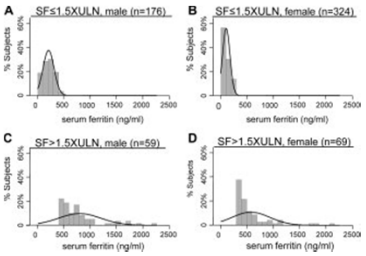
Hepatology
Volume 57, Issue 5, pages 1806-1813, 14 MAR 2013 DOI: 10.1002/hep.26238
http://onlinelibrary.wiley.com/doi/10.1002/hep.26238/full#fig2

Hepatic reticuloendothelial system cell iron deposition is associated with increased apoptosis in nonalcoholic fatty liver disease



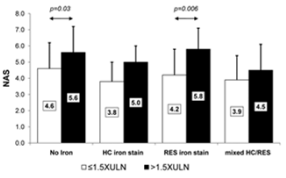
Hepatology
Volume 57, Issue 5, pages 1806-1813, 14 MAR 2013 DOI: 10.1002/hep.26238
http://onlinelibrary.wiley.com/doi/10.1002/hep.26238/full#fig3

Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease



Hepatology
Volume 55, Issue 1, pages 77-85, 6 DEC 2011 DOI: 10.1002/hep.24706
http://onlinelibrary.wiley.com/doi/10.1002/hep.24706/full#fig1

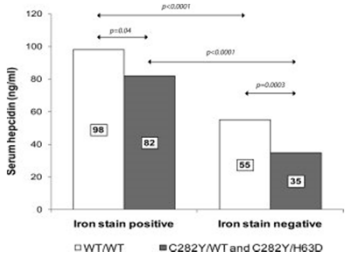
Serum Ferritin Level and NASH



OR Ferritin>2.5= 2.46, p<0.005
For advanced fibrosis

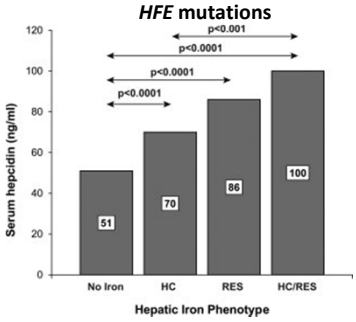
Kowdley et al., Hepatology, 2011

Lower serum hepcidin and greater parenchymal iron in nonalcoholic fatty liver disease patients with C282Y *HFE* mutations



Hepatology
Volume 56, Issue 5, pages 1730-1740, 20 SEP 2012 DOI: 10.1002/hep.25856
http://onlinelibrary.wiley.com/doi/10.1002/hep.25856/full#fig3

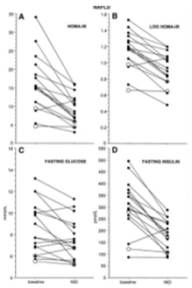
Lower serum hepcidin and greater parenchymal iron in nonalcoholic fatty liver disease patients with C282Y *HFE* mutations



Hepatology
Volume 56, Issue 5, pages 1730-1740, 20 SEP 2012 DOI: 10.1002/hep.25856
http://onlinelibrary.wiley.com/doi/10.1002/hep.25856/full#fig4

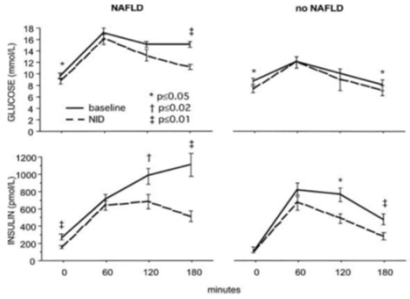
Effect of iron depletion on IR in NAFL

- Changes in insulin resistance measured by HOMA
- No changes in body weight, medications
- Fasting insulin decreased by 40% (p<0.001)
- 3 hour OGTT decreased by >50% (p<0.001)



Facchini et al., Gastroenterology. 2002

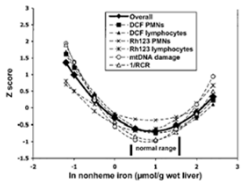
Effect of Phlebotomy in IRS and NAFL



Facchini et al., Gastroenterology. 2002

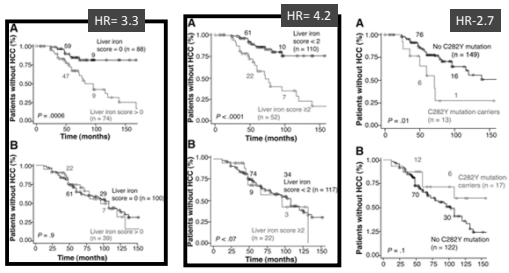
Iron and mitochondria

- Both iron deficiency and iron excess can damage mitochondria
- Iron deficiency resulted in decreased respiration efficiency
- Iron excess resulted in mitochondrial DNA damage



Walter et al., ,PNAS 2002

Liver Iron and HCC risk in HCV, ALD



Any Iron | Score ≥2 | C282Y mutation

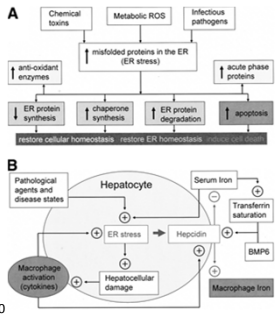
Nahon et al., Gastroenterology 2008

Unfolded Protein Response

UPR are shown that together either restore ER and cellular homeostasisor destroy severely afflicted cells.

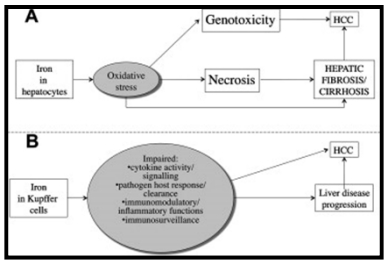
Progression of many liver diseases follows a common course: pathogen-induced ROS, activation ofER stress, recruitment of immune cells, and accelerated liver damage.

Induction of hepcidin by ER stress1 represents a new mechanism linking iron and NASH



Messner and Kowdley Hepatology 2010

Hepatic Iron and Progression in NAFLD



: Journal of Hepatology 2009; 50:249-251

Phlebotomy therapy in NASH

- 31 patients with NAFLD
- Iron depletion until ferritin <50, Hgb<100
- Biopsy pre and post-phlebotomy
  - Significant improvement in NAS score (-0.74,38%)
  - Not in individual components
- Did not support Phase 3 trial

Beaton et al., APT 2013