Role of Iron in ASH/NASH

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Alcohol Consumption and Iron Stores:
NHANES III

<table>
<thead>
<tr>
<th>Prevalence (%) (and SE) in the following alcohol consumption categories (in drinks/day):</th>
<th>Adjusted* OR:</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0-1</td>
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<tr>
<td>Ferritin&gt;300 (men) or Ferritin&gt;200 (women)</td>
<td>8.6 (0.5)</td>
</tr>
<tr>
<td>TS&gt;45%</td>
<td>4.5 (0.4)</td>
</tr>
</tbody>
</table>

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 2.55, 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])

*P* < 0.05 between C282Y+/- and wt patients

*Nelson et al., Hepatology 2007*
Pattern of Iron Deposition and NAFLD Severity

Pattern of Iron Staining and NASH

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

- Figure 1: Comparison of apoptosis rates among No Iron, HC Iron, and RES Iron groups.

- Figure 2: Comparison of MDA and Tn1 levels among No Iron, HC Iron, and RES Iron groups.

- Figure 3: Comparison of M30 and M65 levels among No Iron, HC Iron, and RES Iron groups.
Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease

Serum Ferritin Level and NASH

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

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

Kowdley et al., Hepatology, 2011
Lower serum hepcidin and greater parenchymal iron in nonalcoholic fatty liver disease patients with C282Y HFE mutations

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

Nahon et al., Gastroenterology 2008

Unfolded Protein Response

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

Progression of many liver diseases follows a common course: pathogen-induced ROS, activation of ER stress, recruitment of immune cells, and accelerated liver damage. Induction of hepcidin by ER stress represents a new mechanism linking iron and NASH

Messner and Kowdley Hepatology 2010
Hepatic Iron and Progression in NAFLD

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