Iron Chef: Serving up high quality care in the setting of iron deficiency and iron overload

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May 1, 2020

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Presenter Disclosure

• Speaker’s name: Donald S. Houston

• Relationships with commercial interests:
  – Grants/Research Support: None
  – Speakers Bureau/Honoraria: None
  – Consulting Fees: None
  – Other: I don’t eat their food (and I don’t take iron)
Mitigating Potential Bias

• Not Applicable
Learning Objectives

1. Explain the mechanisms by which the body regulates iron homeostasis, and how defects can lead to iron overload
2. Use simple tests (iron, TIBC, and ferritin) to sort out disorders of altered iron status
3. Apply strategies to manage iron deficiency and iron overload
Appetizer (empty calories)

• Iron makes up a third of the mass of the Earth, and is 4th most abundant element in Earth’s crust (~5%)
• Nonetheless iron is a limiting nutrient that is jealously conserved by the body
• WHO 2011 estimate: anaemia affects around 800 million worldwide (mostly children and women, mostly iron deficiency)
## Distribution of iron

<table>
<thead>
<tr>
<th>Cell type / tissue</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red cells (hemoglobin)</td>
<td>2500mg</td>
</tr>
<tr>
<td>1 unit of PRBCs ≈ 250mg</td>
<td></td>
</tr>
<tr>
<td>Storage (mainly liver, also splenic and bone marrow macrophages)</td>
<td>1000mg</td>
</tr>
<tr>
<td>Enzymes, myoglobin etc.</td>
<td>400mg</td>
</tr>
<tr>
<td>In plasma (bound to transferrin)</td>
<td>4mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4000mg</strong></td>
</tr>
</tbody>
</table>

.005% of body mass
Hemoglobin Structure

Files:
bioinformatics.org/firstglance/fgij/fg.htm?mol=http://www.umass.edu/molvis/bme3d/materials/structures/1hho_quat.pdb.gz&
Heme
Daily Iron Flux

N.B.: there is no means to excrete iron

8mg ♂
18mg ♀ (RDA)

30mg
29mg
1-2mg
Losses
1-2mg
>7mg
non-absorbed
Hepcidin

- Transferrin
- Ferritin
- Iron
- IL-6
- Erythropoiesis (via erythroferrone)
- Hemochromatosis mutations

Reticuloendothelial Macrophage

Intestine

Enteric epithelium

Ferroportin

DMT-1

Transferrin

Hepcidin
Hepcidin regulation

Adapted from Finberg KE. Hematology 2011 pp. 532-7
Warning: Contents may be hot!

Free Radicals

• Free iron is highly reactive
• Generates free radicals by the Fenton reaction:

\[
\begin{align*}
\text{Fe}^{2+} + \text{H}_2\text{O}_2 & \rightarrow \text{Fe}^{3+} + .\text{OH} + \text{OH}^- \\
\text{Fe}^{3+} + \text{H}_2\text{O}_2 & \rightarrow \text{Fe}^{2+} + .\text{OOH} + \text{H}^+
\end{align*}
\]

• Ergo the body must keep iron under very tight control
• E.g. \(K_d\) of transferrin is \(\sim 10^{-20}\)M

Do not memorize!
Safe iron handling

- **Ferritin** is the primary *intracellular* storage protein for iron (the liver is the pantry)
  - 24-subunit spherical cage, tightly sequesters up to 4500 Fe\(^{3+}\) ions
  - More iron => more ferritin synthesized
  - Correlates with amount in plasma, though plasma ferritin has no evident function

- **Transferrin** is the protein that transports iron through plasma to TfR-expressing cells
  - Iron deficiency => increased transferrin synthesis
  - Measured as Total Iron Binding Capacity (TIBC)
  - i.e. \( TIBC = \text{transferrin} \)
Too many cooks...

Iron & Acute phase response

• Inflammatory signals (especially IL-6) trigger changes in hepatic synthesis of many plasma proteins

• Ferritin increases
  – like CRP or fibrinogen

• Transferrin decreases
  – like albumin

• Hepcidin increases
  – Sequestering iron in cells, so serum iron falls
# Tests of Iron Status

<table>
<thead>
<tr>
<th></th>
<th>Iron overload</th>
<th>Iron deficiency</th>
<th>Inflammation</th>
<th>Iron deficiency + inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin</strong></td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>MCV, MCHC</strong></td>
<td>↔</td>
<td>↓</td>
<td>↓ or ↔</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Serum iron</strong></td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>TIBC</strong></td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Tsat</strong></td>
<td>↑**</td>
<td>↓↓</td>
<td>↓ or ↔</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Ferritin</strong></td>
<td>↑</td>
<td>↓**</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Hepcidin</strong>*</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑ or ↔</td>
</tr>
</tbody>
</table>

*not available for routine clinical use  **preferred test

TIBC = total iron binding capacity = transferrin
Tsat = transferrin saturation = serum iron / TIBC
Causes of Iron overload

- Repeated transfusion (except if for bleeding)
- Hereditary hemochromatosis
  - Defect in sensing of iron status
  - Inappropriately low hepcidin
  - Ferroportin stays wide open
  - Increased absorption and release of iron
  - Tsat constitutively high
- Ineffective erythropoiesis (e.g. thalassemia)
  - High erythroferrone levels made by erythroid marrow
  - Suppression of hepcidin
- Advanced cirrhosis
  - Impaired hepcidin synthesis due to liver failure
Hepcidin regulation

Adapted from Finberg KE. Hematology 2011 pp. 532-7
Hereditary hemochromatosis

- Almost 10% of population of northern European stock are carriers of mutations in HFE gene
- 1/400 is homozygous for C282Y
- Lifelong slow iron accumulation, typically not symptomatic until 50’s or 60’s
- Women relatively protected until menopause
- Penetrance (cirrhosis or heart failure) is incomplete
- C282Y/H63D much milder iron loading, very low penetrance
- If fasting Tsat persistently >45%, order HFE genotyping
Rust stains – Toxicities of Iron

- **Liver**: hepatocellular injury (↑ transaminases), cirrhosis, hepatoma
- **Pituitary**: hypogonadism (loss of libido, erectile dysfunction, amenorrhea), hypothyroidism
- **Pancreas**: diabetes
- **Joints**: arthritis classically 2\textsuperscript{nd} and 3\textsuperscript{rd} MCP joints
- **Heart**: congestive failure and arrhythmias
- **Skin**: darkening
- Acute iron poisoning very different
Hemochromatosis - management

• Phlebotomy
  – 500ml = 250mg of iron
  – Bleed q1-2 weeks as Hb tolerates
  – May require 40 or more units removed to reach iron neutral state
  – Once ferritin <100, bleed ~4-6 times/year to keep **ferritin in target range of 50 – 100**
  – Can often meet this need as blood donor
Causes of high ferritin

- Iron overload: the minority!
  - <10% of pts with high ferritin have hemochromatosis
- Inflammation
  - Infections, rheumatologic disorders, renal disease, cancer
- Liver disease esp. fatty liver and alcohol excess
  - Probably *commonest* cause

- *NB: recommended initial test if you suspect hereditary hemochromatosis is Tsat, not ferritin*
- If in doubt, liver iron can be measured by MRI
High Ferritin

Hemoglobin

Abnormal

See Investigation of anemia algorithm

Normal

Obtain Transferrin Saturation (T Sat)
(T Sat = serum iron / TIBC)

> 45%

HFE genotype

C282Y/C282Y (higher risk) OR
C282Y/H63D (lower risk)

Phlebotomy to target ferritin 50-100

In Winnipeg, GIM or community hematolgy have agreed to take on these patients
In rural settings, please arrange phlebotomy at local hospital

< 45%

Other/normal

Assess for:
1. Alcohol use
2. Metabolic syndrome, obesity, DM
3. Liver disease
4. Malignancy, infection, inflammation

Absent

Ferritin >1000?

MRI liver for iron quantitation.
If increased, consider specialist referral (hepatology, GI, hematology).

Follow
Iron Homeostasis: Take home

• Iron status is maintained by regulating the absorption of iron
• All patients with iron overload have elevated ferritin, but most elevated ferritin is reactive
  – Tsat is preferred initial test for diagnosis of hemochromatosis
• All tests (serum iron, TIBC, and ferritin) are influenced by both iron status and inflammation
Ode to hemochromatosis

When your HFE gene code is wrong,
Liver’s T2-star signal gets strong
‘cuz a lack of hepcidin
Has the bowel decidin’
To absorb extra Fe all day long
Thank you

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