Detailed Study Notes

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Introduction to this Episode

Iron is involved in a whole range of biological processes and a consistent supply of iron is crucial for cellular turnover.

But despite iron being an essential mineral for human function, it is highly toxic to cells and tissues if present at high levels. Therefore an intricate and tight regulation of iron is necessary.

If iron status gets too low, iron-deficiency anemia can result. In such situations there is a shortfall in hemoglobin production, which leads to a range of issues in the body.

This leads to many questions, for example:

- So how is iron status measured?
- Which biomarkers are most useful?
- Where can errors in diagnosis occur?
- What problems arise with iron deficiency?
- And what problems occur with iron overload?

In this episode, these questions (and more) are put to Dr. Austin Baraki, a practicing Internal Medicine physician and Assistant Professor of Medicine at William Beaumont Army Medical Center in Texas.

Dr. Baraki was previously on the podcast in episodes 334 and 417:

- 334: Potential Harms of Screening, Overdiagnosis and Overtreatment
- 417: What Do Nutrient Blood Tests Actually Tell Us?: Understanding Biomarkers

[Note: there are a few terms related to this topic that have different spellings in 'US English' and 'UK English'. In these notes, we will default to US spellings for consistency. But just note you may be more familiar with alternative spellings, or see different spellings in research publications, depending on the authors.
***For example:** heme/haem, hemoglobin/haemoglobin, anemia/anaemia]*

Connection to Previous Episodes

#240: Exercise-Associated Anemia, Hepcidin Activity & Implications for Athletes

- In this episode registered dietitian Erica Goldstein was on the podcast to discuss issues related to iron-deficiency, especially in the context of athletes.
- We discussed the symptoms of iron-deficiency anemia, why iron is so crucial for athlete performance, and the role of hepcidin, among other things.
- You can find the episode page here.

#334: Potential Harms of Screening, Overdiagnosis and Overtreatment

- In this episode, Dr. Baraki discusses a range of important and underappreciated issues related to overscreening, overdiagnosis, and overtreatment.
- He got into things like:
    - What do we want from a screening test? What criteria should it meet?
    - Understanding test sensitivity, specificity and predictive value
    - Harms of inappropriate screening or too much screening
    - What tests are appropriate for screening healthy people?
- You can find the episode page here.

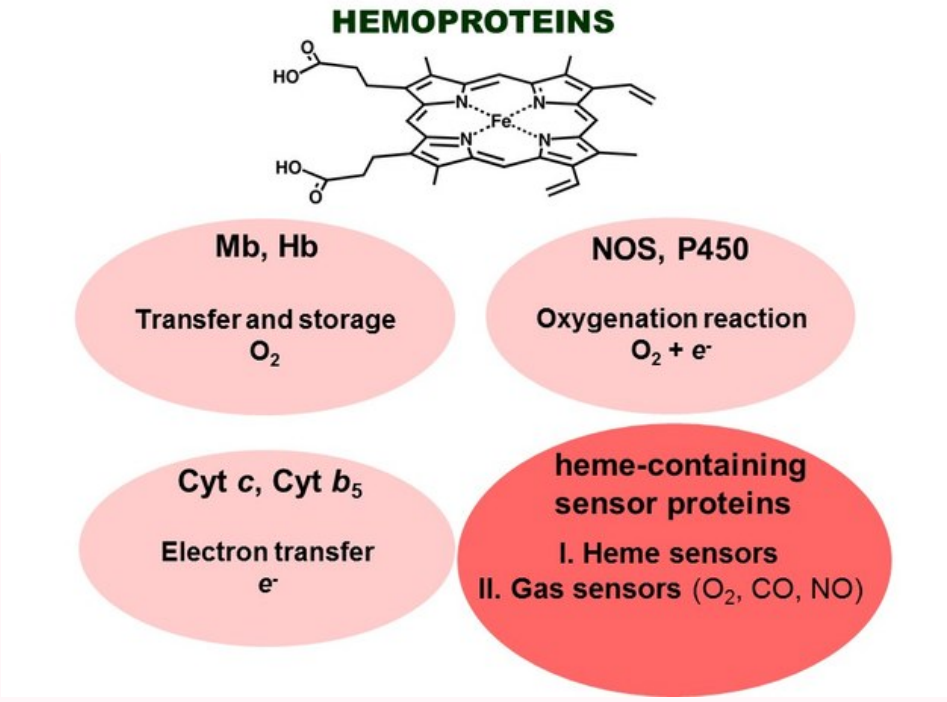
#417: What Do Nutrient Blood Tests Actually Tell Us?: Understanding Biomarkers

- Dr. Austin Baraki joins Danny and Alan to critically evaluate the assumption that blood levels of a nutrient directly tell us about overall nutritional status.
- With many people getting blood tests done outside of clinical settings, there is significant risk of misinterpretation of what these measures mean.
- In this episode we discuss measures of calcium, sodium, vitamin D and others as examples of where misinterpretation and misunderstanding can happen.
- You can find the episode page here.

In addition to these episodes, we have a written Sigma Statement on the website, titled *'Which Micronutrients Do I Need? – Commonly Underconsumed Vitamins & Minerals',* which discusses the prevalence of iron deficiency in developed countries, as well as dietary targets and current intakes.

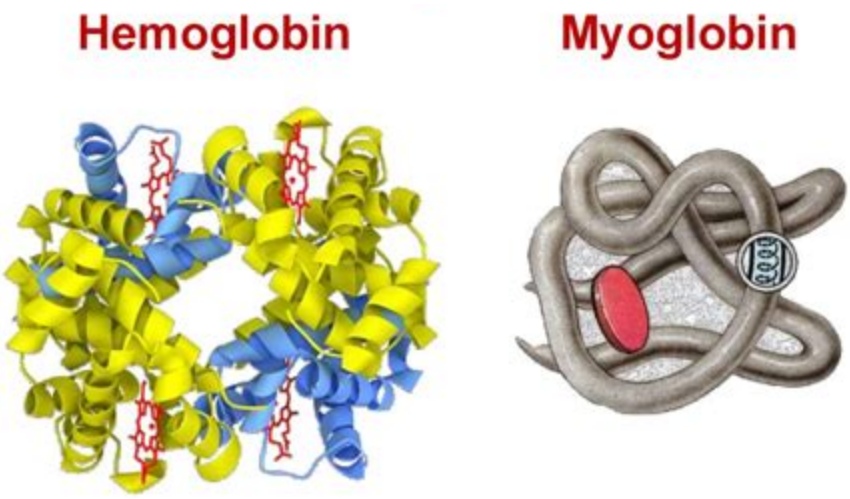
Importance of Iron: Functions in the Body

- The majority of iron is used as part of oxygen binding and oxygen transport.
- Many of the important functions relate to the molecule **heme**.
    - Heme is something that is found in hemoproteins; i.e., proteins that contain a heme group.
    - A heme group itself is composed of iron and another molecule called a porphyrin ring.



Picture from a conference presentation – hemoproteins divided into four main groups.
Author: Markéta Martínková, Source: natur.cuni.cz

- Adequate heme supply is essential for several functions including oxygen transport and storage, energy production and drug metabolism.
- Our red blood cells contain something called **hemoglobin**
    - Hemoglobin contains heme, heme contains iron
    - Binds oxygen
    - Most of the iron in our body is contained in red blood cell hemoglobin (~2,500 milligram)
- Oxygen then gets delivered to our tissues, where the tissues will take it up and use it for oxidative metabolism.



- Hemoglobin has a “cousin” called **myoglobin**
    - Myoglobin performs similar functions to hemoglobin, but specifically in muscle tissues (rather than red blood cells).
- Beyond hemoglobin and myoglobin, smaller amounts of iron can be found in various biochemical pathways (e.g., cytochrome system) and enzymes (e.g. those involved in DNA synthesis of neurotransmitters).

So the principal role of iron relates to oxygen transport and delivery.

Iron Homeostasis

- In healthy adults, iron is lost daily, primarily due to blood losses.
    - There is also loss of iron from the constant exfoliation of iron-containing epithelial cells that line the gastrointestinal and urinary tracts, skin and hair.
- Therefore, the same amount of iron from dietary sources is required each day to replace the lost iron and maintain body iron homeostasis.
- Despite iron being an essential mineral for health, it is highly toxic to cells and tissues if present in elevated levels.
    - But, humans do not possess the necessary machinery to rid the body of excess iron,
    - Therefore, iron absorption needs to be very tightly regulated in order to avoid both iron deficiency and overload.

"This demand and the need to avoid the potential toxic effects of free iron are met by a rigorously regulated system that controls the rate of iron absorption, maintains a store of readily available iron and recycles iron derived from cells at the end of their life spans." – Lynch et al., 2018

Iron homeostasis is achieved by the combination of regulation at two levels:

1. **Systemic iron homeostasis:** Iron supply is regulated by keeping the plasma iron level within a fairly narrow range.

2. **Cellular iron homeostasis:** Individual cells have the ability to adjust the amount of iron they import and to store any excess.

Transferrin is the major vehicle for iron delivery to cells and is present in the circulating plasma and extravascular fluid.

- Most of the iron entering the plasma pool (~22 mg/d) is derived from the reprocessing of heme in red blood cells that have reached the end of their life spans (about 90 –120 days)
- Absorption from the diet contributes only ~1 mg/d in an iron-sufficient adult man.
- Pre-menopausal women absorb a little more, ~1.5 mg/d, to compensate for menstrual blood losses.
- In healthy adults, some 0.5 - 2.0 mg of iron is lost each day due to blood loss and turnover of cells lining the gastrointestinal and urinary tracts, skin and hair.

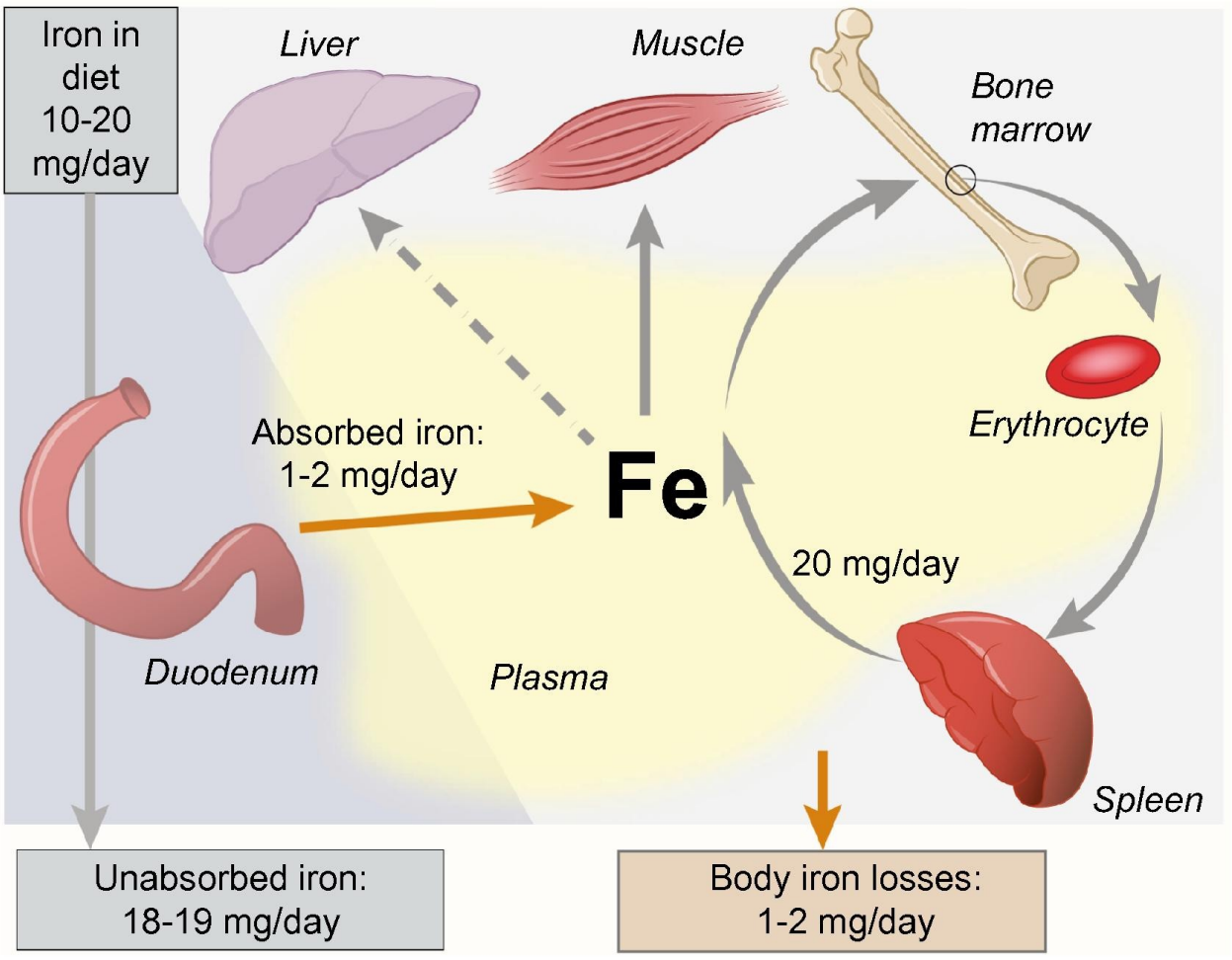
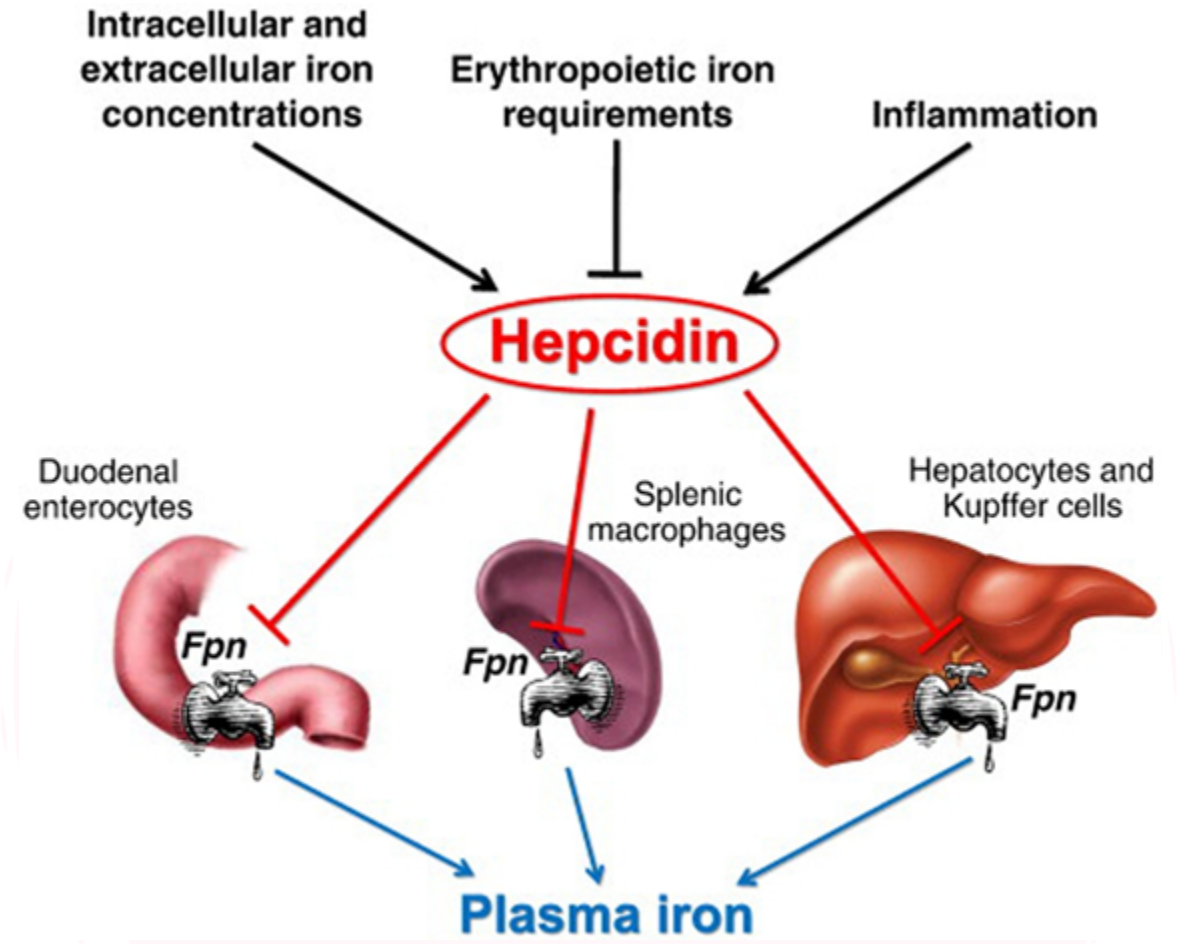


Image from: Brissot & Loréal, J Hepatol. 2016 Feb;64(2):505-515.

Hepcidin

- **Hepcidin** is a liver-derived, iron-regulating peptide hormone
- "It controls the delivery of iron to blood plasma from intestinal cells absorbing iron, from erythrocyte-recycling macrophages, and from iron-storing hepatocytes." (Ganz et al., 2016)
- It binds **ferroportin** transporters at the small intestinal cells and blocks them from being able to export iron into the bloodstream. So it directly blocks iron absorption.
- When hepcidin is high, it limits iron export into the plasma.
- Hepcidin activity goes up or down depending on the needs of the human:
    - So when iron deficient, or when using lots of iron during periods of growth (e.g., during adolescence or pregnancy), hepcidin is going to be suppressed because you need more iron.
    - On the other hand, hepcidin can be upregulated in a few situations, most notably during periods of **inflammation**.
        - When hepcidin is high due to chronic inflammation (e.g., with long-term disease states), the patient does not necessarily have true iron deficiency, but they end up *functionally* iron deficient because all of the absorption is being blocked.

Hepcidin-ferroportin (Fpn) interaction determines the flow of iron into plasma. Hepcidin concentration is in turn regulated by iron, erythropoietic activity, and inflammation:



From: Ganz & Nemeth, Biochim Biophys Acta. 2012 Sep;1823(9):1434-43.

Hemochromatosis

- **Hereditary hemochromatosis** is a genetic condition where you have mutations in the HFE gene leading to inappropriately low hepcidin levels.
- So if that's not being suppressed, then ferroportin continues to take up lots of iron, which is transported into your bloodstream.
- So there's inappropriate over-absorption of iron, leading to iron overload/excess.

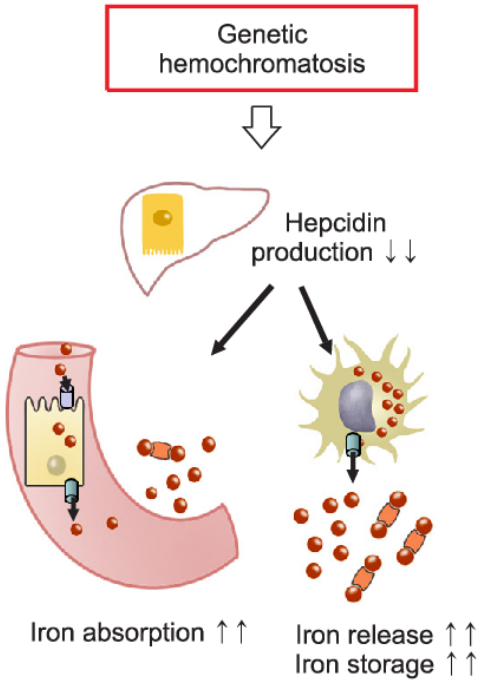


Image from: D'angelo, Blood research 2013; 48(1): 10-15.
© 2013 Korean Society of Hematology

- Hereditary hemochromatosis occurs in Caucasians of Northern European decent.
- The increased iron deposition in several tissues—particularly the liver, but also the pancreas, heart and synovial tissue— can result in tissue damage through production of reactive oxygen species (Fairweather-Tait and Sharp, 2021).
- It is often seen as a "silent disease" as many of the symptoms are associated with more common conditions of aging including: fatigue, arthritis, erectile dysfunction, diabetes and cardiac disease.
- Nickname of "Bronze Diabetes" due to tanning of the skin and potential for diabetes.
- The standard treatment for HH is phlebotomy, in which 500mL blood is removed every 1–2 weeks until serum ferritin levels fall to within the normal range.
- This is followed by maintenance phlebotomy every 3–6 months.
- Diet can play some role in treatment but is not a replacement for phlebotomy.

Biomarkers & Testing

If somebody has no symptoms whatsoever, iron status is ***not*** something that is recommended to be screened by default in healthy adults, who are not pregnant.

In cases where there is enough reason to check iron status, then the typical initial testing that's going to be done is a **complete blood count (CBC)**.

- CBC measures our white blood cell count, our hemoglobin level platelet, and a many other parameters that are descriptive of our red blood cells (e.g. size, hemoglobin content, etc.).
- So a complete blood count can help us determine:
    - Does somebody have anemia? Is their hemoglobin below 12 grams per deciliter in women?
    - Are their red blood cells really tiny? Are they really variable in width?
- There will also be values for MCV, mean corpuscular volume, or the red cell distribution with RCD.

After a CBC, there is an **iron panel**. And an iron panel contains a few different things:

- **Ferritin**
    - the storage form for iron
- **Total iron binding capacity**
    - a descriptor of our transferrin situation, the protein that carries it around in the bloodstream.
- **Transferrin saturation**
    - If you take the iron level and you divide it by the total iron binding capacity, you get the transferrin saturation.

There are many potential biomarkers of iron status. But any measure in isolation comes with disadvantages (as seen over the page). Therefore diagnosis shouldn't be made on any isolated test result. Rather they should be placed in the context of the patient's background, medical history, presenting symptoms, diet, and other test results.

Crucially, as Dr. Baraki emphasized: ***"if you find iron deficiency, you must explain it."***

Established biomarkers	Disadvantages
Bone marrow iron	Invasive
Hemoglobin (Hb)	Low specificity and sensitivity
Hematocrit	Low specificity and sensitivity
Erythrocyte protoporphyrin (or zinc protoporphyrin)	Inaccurate, affected by lead exposure
Serum iron, TIBC, transferrin saturation	Variations caused by food intake, circadian rhythms, and infection, inflammation and disease (IID)
Reticulocyte Hb content	Requires expensive laboratory equipment
Mean cell volume (MCV)	Requires expensive laboratory equipment, affected by IID
Red cell distribution width	Requires expensive laboratory equipment, affected by IID
Mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin content (MCHC)	Low specificity
Serum ferritin (SF)	Acute phase protein, does not reflect iron stores in the presence of IID
Soluble transferrin receptor (sTfR)	Affected by rate of erythropoeisis

From: Fairweather-Tait and Sharp, chapter 7 in: *Advances in Food and Nutrition Research*, Vol 96, 2021 Pg 219-250.

Anemia

Anemia develops over prolonged periods where iron supply to the bone marrow for synthesis of hemoglobin does not meet metabolic demand.

There are typically three stages described for the development of iron-deficiency anemia:

1. **Iron depletion**
    a. The levels of storage iron are reduced
    b. Typically assessed by serum ferritin concentration
2. **Iron-deficient erythropoiesis**
    a. There is a restricted iron supply to the bone marrow leading to mild tissue deficiency
    b. Reduced transferrin saturation and increased soluble transferrin receptor and erythrocyte protoporphyrin are often used here
3. **Iron deficiency anemia**
    a. The production of functional iron containing compounds is compromised (low Hb).
    b. In situations of chronic disease, anemia can develop without an initial iron deficiency (anemia of chronic disease)

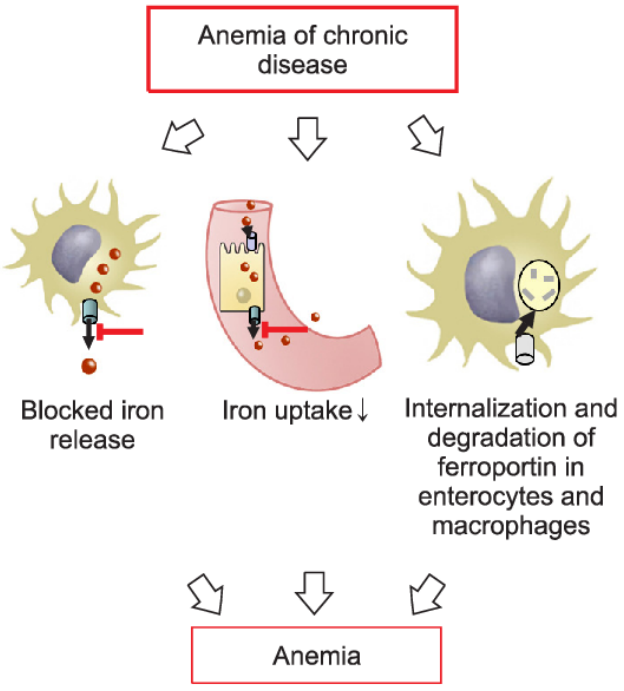


Image from: D'angelo, Blood research 2013; 48(1): 10-15.

Ganzoni Equation for Iron Deficiency Anemia

Associations with Iron Deficiency

- **Pica** is the eating or craving of things that are not food. The ingested or craved substance may be biological, natural or manmade. Often associated with iron deficiency but its pathophysiology is unknown (Borgna-Pignatti & Zanella, 2016).
- "**Beeturia**, the passage of pink or red urine after the ingestion of beetroot, is said to occur in 10-14% of the population, and is more common in iron deficiency and malabsorption." (Watts et al., 1993)
- **Restless legs syndrome** is characterized by an uncomfortable urge to move the legs while at rest, relief upon movement or getting up to walk, and worsened symptom severity at night. RLS may be primary (idiopathic) or secondary to a variety of systemic disorders, especially iron deficiency (Gossard et al., 2021)

Correct Diagnosis & Interpretation

- Dr. Baraki outlined a simplified framework to start thinking about why anemia is present: **'iron in' versus 'iron out'.**
- **Iron-in:**
    - **Diet:** Are they consuming enough?
    - **Absorption:** Once iron gets down to the stomach, what's happening? Is it getting absorbed or not?
        - Could they have low or suppressed stomach acid? (e.g. they're taking lots of acid-suppressing medications)
        - Do they have a problem anatomically or physiologically with their stomach? Have they had bariatric surgery or metabolic surgery and had part of their stomach or small intestine taken out?
        - Undiagnosed disorders:
            - Chronic infections such as h. pylori infection
            - Autoimmune conditions like pernicious anemia or celiac disease
- **Iron-out (i.e., blood loss):**
    - Where could blood loss be occurring?
        - The most common is anywhere in the gastrointestinal tract
        - Are you throwing up any blood? Are you having blood in your stools?
    - Possible endoscopic evaluation
    - Colonoscopy to look for evidence of colon cancer or colon polyps
    - Diverticula and hemorrhoids.
    - Endurance athletes: repeated impact hemolysis (see episode 240)

Treatment

- Supplementation
    - Ferrous sulfate is commonly used
    - Avoid using slow-release, enteric coated supplements
        - Iron gets absorbed principally in the proximal duodenum. So if you have an enteric coated iron formulation that is in a capsule that is slow release, it's going to get all the way to the end of the intestine before it's fully broken down.
- If not responding to supplementation, IV iron may be an option. However, it's not available in many places and some doctors are hesitant to use it.